Upper Limb Movement After Hemispherectomy

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DOCTOR OF PHILOSOPHY

I, David Robert Henry Nobbs, confirm the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in the thesis.

1st March 2018

Signed: ..... Date: .....

Abstract

Hemispherectomy is a surgical procedure for treating intractable epilepsy, involving the removal or disconnection of a cerebral hemisphere. Prior to surgery, patients have weakness along one side of their body and disruptions to their motor control. These impairments can be further exacerbated by the operation. This thesis provides an investigation into upper limb movement after surgery in terms of gross motor control and ipsilateral descending motor pathways for distal function. A neurophysiological assessment was used to identify the pathway driving the distal muscles of the paretic upper limbs. The results support the findings of previous studies that suggest superior function is likely to be dependent on a common, branching corticospinal pathway to the left and right sides. In addition, one patient without evidence of a common pathway had some use of the paretic wrist suggesting the presence of a distinct ipsilesional – possibly corticoreticulospinal – pathway. Upper limb kinematics during functional unimanual and bimanual reaching was also assessed. Unimanual deficits were identified and abnormalities in inter-limb coordination were found. These include a tendency to perform bimanual reaches as sequential unimanual reaches and reduced spatial interference in the trajectories of the two limbs. Whilst there were significant differences between the comparison and patient groups for these measures, there was also significant variance between the patients, underlining the heterogeneity of this cohort.

Impact statement

The results of the studies in this thesis are expected to impact academic research into ipsilateral motor control after hemispherectomy. Firstly, neurophysiological studies can be pursued to further understand the two potential patterns of motor reorganisation that may underlie distal upper limb function. Secondly, neuroimaging studies can be pursued to understand the neural structures and connectivity involved in bimanual coordination with a single hemisphere. The results of this thesis have already been communicated to academic audiences through poster presentations at academic conferences. The results are planned to be disseminated further through the submission of manuscripts to academic journals.

Furthermore, the methods used in this thesis can impact the clinical motor assessment of patients who undergo hemispherectomy. The positive findings of the neurophysiological assessment can impact the pre-operative assessment of hemispherectomised patients. The results of the kinematic assessment demonstrate its feasibility as a performance outcome measure of functional reaching in hemispherectomised patients that can be used in clinical practice. The results have already been communicated beyond academia through talks at epilepsy workshops involving clinicians from many different areas. In the future the validity and reliability of the methodologies can be established through collaborations with healthcare professionals working in the pre- and post- operative assessment of hemispherectomy candidates.

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1. General introduction

1.1 Hemispherectomy as treatment for intractable epilepsy

An epileptic seizure is defined as a transient occurrence of symptoms due to abnormal and excessive synchronous neuronal activity in the brain (Fisher et al. 2005). The behavioural symptoms are determined by the functions of the areas of the brain where the neuronal activity originates from and spreads to. They might include impaired cognitive function, involuntary movement, sensory experiences and autonomic disturbances. When the propensity for epileptic seizures endures over time, the condition is diagnosed as epilepsy. It is estimated that around 50 million people have epilepsy worldwide (WHO 2001) and, in the UK, approximately 1 child in every 220 is known to suffer from the disease (JEC 2010). In developed countries, epilepsy incidence is highest in the first year of life (Forsgren et al. 1996).

There are many possible causes of the neuronal activity associated with epilepsy (Berg et al., 2010). If a genetic disorder gives rise to a cerebral lesion, which in turn causes epileptogenic disturbances, then the disorder is not strictly categorised as one of genetic epilepsy, rather it may be termed a genetic disorder associated with epilepsy. One such example is hemimegaencephaly – a malformation of cortical development that involves the enlargement of one cerebral hemisphere. A second is Sturge-Weber syndrome – a progressive disorder characterised by a facial birthmark, involving the development of excessive blood vessel growth on the surface of the brain. If epileptic seizures are manifestations of a pathology that is specifically structural or metabolic, it may be classified as acquired. Acquired epilepsy disorders are caused, most often, by prenatal or perinatal brain damage (Engel 2013). Brain damage may be due to hypoxia, physical trauma or an infection. If the cause of epilepsy is unknown, the disorder is categorised as unknown.

Epilepsy may be treated with anti-epileptic drugs. There are many different drugs and selection of the most appropriate for the individual will depend on the type of seizure along with the patient's age and gender, other medical

issues and possible side effects. If the seizures are resistant to the medication, then a second drug may be tried. In adult practice, epilepsy is defined as ‘drug-resistant’ or ‘intractable’ after the failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic schedules (Kwan et al. 2010). In paediatric practice, if the seizure frequency is high, many different medications may be tried over a shorter time-scale (Cross 2002).

When epilepsy proves to be drug-resistant, neurosurgery may be recommended, but this must follow a comprehensive pre-surgical evaluation. There are two main aims to this evaluation. The first is to identify the brain area from which the abnormal neuronal activity appears to originate. This area is referred to as the ‘epileptogenic zone’. Attempts to identify the focus are made through analysis of the spatial distribution of discharges recorded with electroencephalography (EEG), along with other neuroimaging methods and diagnostic tests. An epileptic seizure arising from within one area of one hemisphere is called a focal seizure (Berg et al., 2010). If the activity appears to rapidly engage all parts of the brain simultaneously, then it is referred to as a generalised epileptic seizure. If the brain area responsible for the seizures can be identified, then a resection may be considered, involving the removal or disconnection of the area of the brain from which seizures have been shown to originate

The second aim of pre-surgical evaluation is to determine whether removal or disconnection of this area is likely to compromise function. The majority of focal procedures are directed at the removal or disconnection of the temporal lobe of the cerebral cortex, with a minority directed at extra-temporal areas (Cross 2002). If a patient has a neurological structural abnormality that is considered epileptogenic, too large for a focal procedure, but is present only in one hemisphere of the cortex, then the clinical team may propose carrying out a hemispherectomy or hemidisconnection. This may involve either the removal of an entire cerebral hemisphere (Dandy 1928) or a cerebral resection with disconnection rather than removal of the frontal and occipital poles (referred to as a ‘hemispherotomy’) (see Figure 1). Hemispherotomy

approaches include trans- and perisylvian and vertical parasagittal techniques. Disconnection techniques are often preferred, as they are believed to reduce the risk of postoperative hydrocephalus and hemosiderosis (accumulation of fluid and iron in the brain, respectively) although the probability of seizure freedom is greater after total resection (Griessenauer et al. 2015).

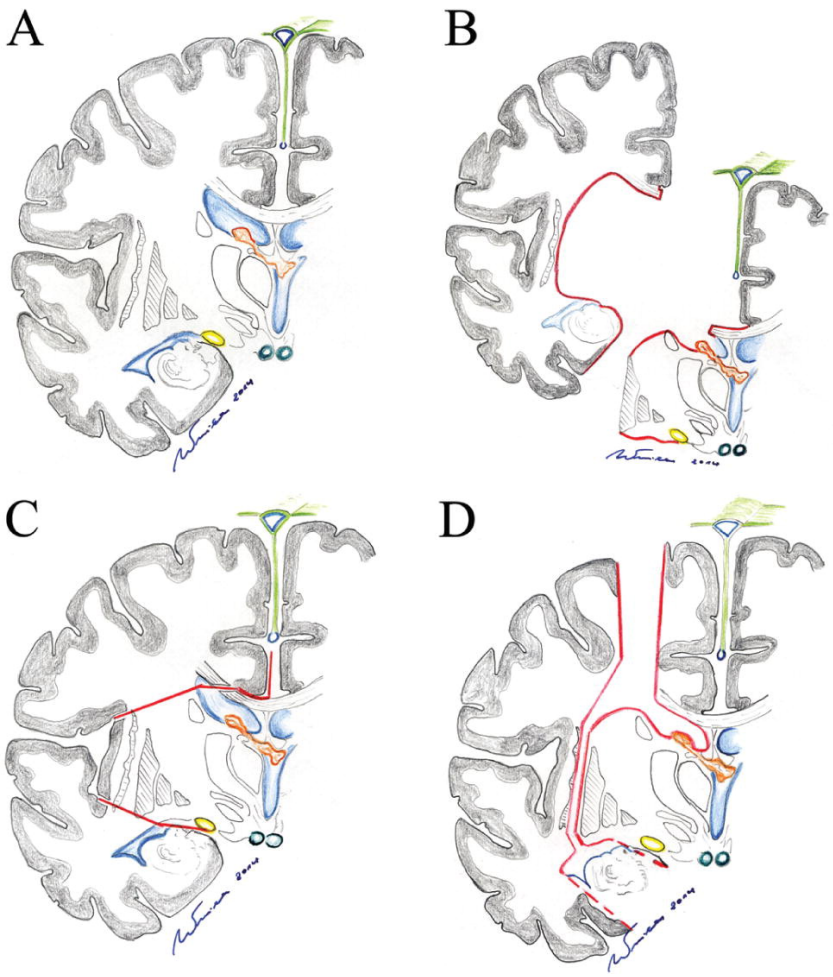

Figure 1. Schematic drawing of the types of hemispherectomy

Illustration by Peter Winkler (Griessenauer et al. 2015). A: Coronal view of the brain at the level of the mammillary bodies. B. Functional hemispherectomy (Rasmussen 1983). C: Trans and perisylvian technique (Villemure and Mascott 1995). D: Vertical parasagittal technique (Delalande et al. 2007). Copyright Peter Winkler.

Patients that are being considered for hemispherectomy already suffer from a variety of motor impairments. These can be revealed with a neurological examination. They may include, firstly, loss of strength on the contralesional side of the body. Secondly, hypertonia, defined as an abnormal increase in steady state muscle contraction. Hypertonia can present itself clinically through exaggerated reflexes, muscle stiffness and spasticity (Bell and Karnosh 1949). Neuromuscular impairments can also lead to, thirdly, musculoskeletal impairments (Ueki 1966). Subluxations (dislocation at a joint) may occur due to hypotonia or paresis, whilst contractures (shortened muscles) may be caused by hypertonia. Contractures and subluxations lead to joint stiffness, whilst hypertonia results in muscle stiffness. All three can contribute to the loss of range of motion that the patient may encounter (van Empelen et al. 2004).

Immediately after hemispherectomy, the patient may find the arm contralateral to the operated hemisphere is hypotonic, i.e. flaccid (Engel et al. 2007). If motor reorganisation has occurred, flaccidity may improve within a month (Gardner et al. 1955; Jellinger 2001). In some cases spasticity is partially relieved by the operation (Krynauw 1950; Zülch and Micheler 1978) and, in the long-term, the motor function of some patients may be improved by surgery (van Empelen et al. 2004). Relatively high functioning cases may even be able to perform useful tasks with the hand contralateral to the resected hemisphere, such as turning the pages of a book or holding a knife and fork (Zülch 1974).

Whilst deficits in the contralesional arm are well known, motor impairments can also be found in the ipsilesional arm. This arm is often referred to as ‘the unaffected/unimpaired arm’ (Carr 1996; Choi et al. 2010; Steenbergen et al. 2000b), but these terms are misleading. Colebatch and Gandevia (1989) showed that in adult stroke patients with hemiparesis, force from the arm ipsilateral to the lesion was impaired, most profoundly for the proximal muscles and this was confirmed for hemispherectomised patients by Dijkerman et al. (2008). Dijkerman et al. also found the ipsilateral arm to be impaired in terms of strength and tapping speed. This may be because the

proximal muscles receive bilateral projections, the ipsilateral component of which could be disrupted by a unilateral cortical lesion. There has been little research into hemispherectomised patients, but tests of dexterity have detected deficits of the ipsilateral arm in patients with hemiplegic cerebral palsy and adult stroke, including tapping (Prigatano and Wong 1997) and sorting pegs (Desrosiers et al. 1996). Findings have not been consistent between studies (Haaland and Harrington 1994), though, and deficits may only be present in some patients: from a sample of 20 hemiplegic children, only 30% showed impairment of the ipsilateral upper limb when carrying out a peg-sorting task (Dellatolas et al. 2005).

1.2 Existing measures of upper limb function

Methods used to assess motor impairments before and after hemispherectomy have changed over time. Prior to the 1990s, published studies on the motor ability of hemispherectomised patients were often written by one or two physicians who provided descriptive accounts of neuromuscular and musculoskeletal impairments, often mentioning some functional tasks that the patient(s) could perform (Bates 1953; Bell and Karnosh 1949; Gardner et al. 1955; Griffith 1967; Krynauw 1950; White 1961; Zülch 1974). There was then increased reporting of standardised measures of dexterity (such as tapping speed and peg sorting) and strength (Dijkerman et al. 2008; Graveline et al. 1998; Holloway et al. 2000; Vargha-Khadem et al. 1997). More recently the trend has shifted toward the reporting of standardised clinical outcome assessments of motor function and impairment. These include the Fugl-Meyer Assessment (Bode et al. 2005; Bode et al. 2009; Choi et al. 2010; Liang et al. 2013), Manual Ability Classification System (Hamad et al. 2013), the Actual Amount of Use Test (Bode et al. 2009), the Movement-ABC (van Empelen et al. 2005), the Gross Motor Function Measure (van der Kolk et al. 2012; van Empelen et al. 2004; van Empelen et al. 2005), the Paediatric Evaluation of Disability (van Empelen et al. 2004; van Empelen et al. 2005) and the Scales of Independent Behaviour Revised (Basheer et al. 2007). These tests may sometimes include a separate measure of muscle tone, i.e. the Modified

Ashworth Scale (Honda et al. 2010; van Empelen et al. 2004) and/or range of motion, i.e. the Joint Alignment and Motion Scale (van Empelen et al. 2004). Descriptions of each individual's motor function and impairment are often provided too (Honda et al. 2010; Kamida et al. 2003; Leonhardt et al. 2001; Pascoal et al. 2013; Rath et al. 2008; Rutten et al. 2002; Zsoter et al. 2012).

Clinical outcome assessments can be categorised as single item, where a single score is assigned to the patient (tapping speed, peg-sorting, the Modified Ashworth Scale); or multiple item, where the patient is scored on multiple elements whose scores are combined, possibly through addition (all clinical outcome measures listed above). Single item scales can be problematic because, if a patient's score is considered on the boundary of two levels, repeated measures by the same or different raters may lead to substantially different conclusions (Haas et al. 1996; Hobart et al. 2000; Hobart et al. 2007). By combining scores of multiple items, one can reduce the error associated with the measurement tool, but multiple item scales retain some problems of the single item method. Most methods use ordinal variables and these are problematic because it is assumed that differences between two levels are equal (Hobart et al. 2007). This is a difficulty for single item methods, since differences between levels are assumed to be equal within an item, e.g. the Modified Ashworth Scale assumes that the difference between spasticity scores of 0 and 1 is the same as the difference between 1 and 2. Multiple item methods extrapolate the problem by also assuming equal differences between items, e.g. the difference between scores of 0 and 1 for elbow flexor reflex activity on the Fugl-Meyer assessment is assumed to be equal to the difference between 0 and 1 for wrist stability.

A second issue, relevant for both single and multiple items measures, is the possibility of floor and/or ceiling effects, i.e. lower/upper limits to a scoring system beyond which the variable of interest is no longer measured. Previous studies of the strength and dexterity of hemispherectomised patients have had difficulties with floor effects, with either all or most patients scoring zero on many measures (Dijkerman et al. 2008; Holloway et al.

2000). Similarly, patients will often attain the lowest scores on elements of multiple item measures or form clusters in the lower range of the scale (Hamad et al. 2013). Clustering can be problematic if it is around only a few levels, as the measurement tool may be unable to detect differences between individuals.

Floor effects and clustering may be related to the choice of method. In the studies listed above the clinical outcome assessments that were used to assess hemispherectomised patients were designed for other cohorts: for assessing adults who have suffered a stroke (Actual Amount of Use Test; Fugl-Meyer Asssessment; Action Research Arm Test), for assessing children with cerebral palsy (Manual Ability Classification System; the Gross Motor Function Measure), for screening children for mild to moderate motor dysfunction (Movement-ABC) or for assessing individuals with a variety of physical and/or behavioural conditions (Scales of Independent Behaviour Revised; Paediatric Inventory of Disability). If one considers that the extent of brain damage after hemispherectomy is roughly equivalent to the most severe form of unilateral cerebral palsy/stroke, then in terms of motor ability hemispherectomised patients are likely to be more closely related to the more severely affected patients. This could, therefore, lead to floor effects or clustering. If a clinical outcome assessment is going to be used on a cohort that it has not been developed for, then it is important to consider if the method is sensitive enough to detect differences between patients.

1.3 Optical motion capture

Whilst clinical outcome measures are now used widely, motion capture technology has become increasingly popular for patient assessment. To understand the benefits of motion capture it is instructive to first appreciate the principles of the method. These principles can be traced back to the early 20th Century, when Otto Fischer pioneered the approach. The most famous of the early adopters was Nikolai Bernstein. For Bernstein's first experimental work he analysed the movements of a worker cutting metal with a chisel (see Figure 2). The position of the worker's hand was registered by placing a light

bulb on it and recording the performance of the striking action with a camera. The light emitted by the bulb left a trace on the film and this trajectory could then be analysed. Bernstein developed this approach further for the analysis of sporting activities, such as those of a gymnast. By placing lights on many different segments of the body of a subject and recording with a shutter frequency of up to 200 frames per second, Bernstein was able to estimate the trajectory and velocity of fast movements of multiple segments of the subject's body. This method became known as cyclography. In order to reconstruct the trajectory of movement in three dimensions, Christian Braune and Otto Fischer began making simultaneous recordings with multiple cameras. Bernstein instead used a single camera to record movement from three different angles, by placing mirrors within the field of view of one camera.

Since these early steps in the recording and analysis of human movement, other methods have been developed using inertial, mechanical or electromagnetic systems, but the use of light remains popular with optical motion capture. Modern optical motion capture has many similarities with early cyclography, although advances in technology allow more precise recordings that are less labour intensive to acquire and analyse. Cameras are now digital, with light sensors and circuitry that convert light energy to voltage and then to digital data. A subject's movement is tracked by reconstructing the trajectory of markers that have been placed on the subject's body. These markers may be active or passive. Similar to the light bulbs used by Bernstein, an active marker emits light from a light emitting diode (LED), whilst passive markers reflect light pulses from a strobe. The strobe light is not visible to the human eye and is emitted from LEDs that are integrated into the camera. When the light pulses are reflected back into the camera they effectively appear to the camera as light sources. Based on the light sources detected by the camera, the camera calculates the centre-point coordinates and size of the visible markers in real time, before transferring this 2D information to a computer.

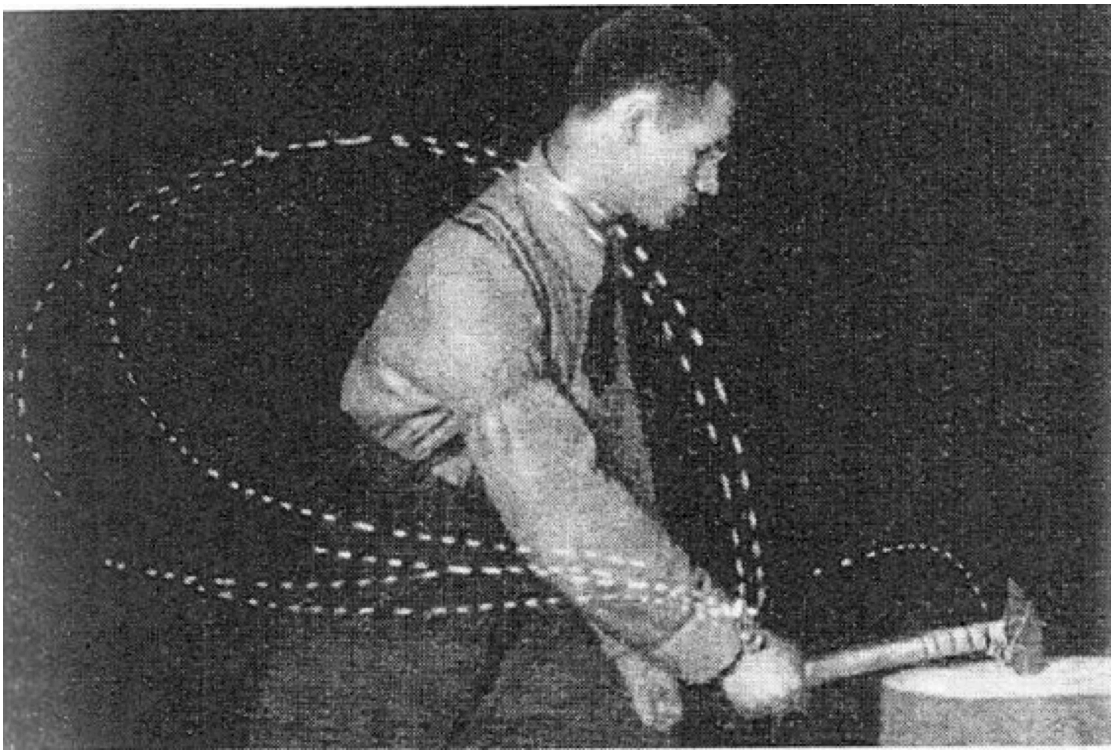

Figure 2. From Bernstein's analysis of a worker’s kinematics

As with the method of Braune and Otto, the 3D position of the markers can be determined from the triangulation of 2D information collected by multiple cameras. To perform this calculation, it is necessary to know how the 2D information from one camera relates to the others, by determining the relative position and orientation of each camera. This process is known as ‘calibration’. A reference structure, with markers separated by known dimensions, should be placed within the field of view of all cameras. Since the relative position of the markers is known, it is possible to calculate the relative orientation and position of each camera. It is then possible to triangulate the 2D positions of a marker over time and so track the marker’s 3D trajectory. But, while a single point in space can be fully described by its 3D coordinates, a physical body, such as a cup, a car or a hand, also requires knowledge of its rotation angles. This can be calculated by placing multiple markers on a rigid body so that the distances between each of the markers remain constant during the measurement. This requires at least

three markers, not all in the same line. With this information it is possible to estimate both the position and orientation of the rigid body in 3D space.

Whilst for some recordings all markers may be visible to at least two or more cameras throughout, behavioural testing may take place in less than ideal conditions. A fundamental difficulty with optical motion capture is, therefore, the possibility of occlusion. When occlusion occurs there is the possibility of interpolating the position of the markers, a process referred to as ‘gap-filling’. Once the trajectory of the markers has been defined, one may wish to analyse the data, but an analysis of the raw data is likely to be influenced by small errors (noise) that may have occurred during the measurement process. To remove unwanted noise, the data can be smoothed by either attenuating frequency components in the signal greater than that expected for voluntary movement with a low pass filter, or by estimating a smooth curve through the data with polynomial regression.

Using motion capture as an assessment tool for patient movement avoids many of the problems associated with clinical outcome measures, providing high quality, objective and consistent measurements. Since variables tend to be on continuous scales the difficulties associated with ordinal scales are normally avoided and – as long as participants can perform the task – floor and ceiling effects are unlikely. The metrics recorded – speed, curvature, number of movement units – are different from those that are available from standardised clinical outcome measures. One could therefore build a more complete picture of a patient’s condition by combining the two approaches.

1.4 Ipsilateral motor control

1.4.1 Corticospinal projections

If severe hemiplegia is already apparent prior to hemispherectomy, then it is presumed that the motor cortex in one hemisphere is already significantly damaged and it can be removed or disconnected without the operation itself inflicting substantial motor weakness (Griessenauer et al. 2015). If, on the other hand, the patient has a less severe hemiparesis, then there may be a

greater risk that surgery will cause further disability. The degree of risk is presumed to depend upon the extent to which the remaining hemisphere has control of the ipsilateral side of the body. This is dependent on the organisation of the descending motor pathways.

The brain transmits motor commands to the spinal cord through a complex system of motor pathways with both ipsilateral and contralateral terminations. The largest of the descending motor pathways – and that which provides the cortex with direct access to the cord – is the corticospinal tract. Most corticospinal neurones project to the contralateral side of the spinal cord. They travel through the posterior limb of the internal capsule and via the cerebral peduncles. Most (~85%) cross the midline at the pyramidal decussation within the medulla and descend through the spinal cord in the dorsolateral funiculus (Davidson et al. 2007). A smaller group (~15%) do not decussate in the brainstem. Instead they descend along the spinal cord in the ipsilateral lateral or ventromedial funiculus. However, these neurones do not necessarily terminate on the same side of the spinal cord that they enter. In the macaque, populations of both crossed and uncrossed corticospinal neurones re-cross the midline as they descend, with some neurones arborising to form branched pathways with bilateral terminations, and terminating in both cervical and lumbar segments of the cord (Lacroix et al. 2004; Rosenzweig et al. 2009; Yoshino-Saito et al. 2010). Whether any ipsilateral projections contribute to hand and digit function is not entirely clear. Conventionally it is thought not, but stimulation studies in the macaque give evidence both for (Boudrias et al. 2010) and against (Soteropoulos et al. 2011).

Whilst corticospinal neurones predominantly terminate in the intermediate zone of the spinal cord, a minority synapse directly onto motoneurones in the ventral horn (corticomotoneurones). Corticomotoneurones have been shown to exist, to varying extents, in the different primate species (Lemon and Griffiths 2005). Brain stimulation studies have supported their existence in humans too (de Noordhout et al. 1999; Palmer and Ashby 1992). Tracing, stimulation and single cell recording studies of the macaque suggest

corticomotoneurones support skilled movement of the hand and digits (Lemon 2008) and, across primate species, there is a correlation between the density of corticomotoneuronal connections and the index of dexterity (Heffner and Masterton 1983). The extent to which they are required for skilled hand and digit function is unknown though since, to date, there is no means of selectively lesioning or inactivating this direct pathway (Lemon 2008). Furthermore, there is only evidence that corticomotoneurones contribute to contralateral distal upper control: whilst one study found some direct ipsilateral terminations in the ventral horn of the macaque, this was in the T1 segment of the spinal cord, amongst medial motorneurones associated with axial motor control (Rosenzweig et al. 2009).

Current evidence indicates that, in the macaque, the proportion of ipsilateral to contralateral corticospinal projections in the adult does not differ from that at birth (Galea and Darian-Smith 1995; White 1961). This contrasts sharply from the cat. In the kitten, at ~3-7 postnatal weeks, corticospinal terminals are distributed widely and bilaterally at all levels of the spinal cord (Boessenkool et al. 1998; Li and Martin 2000; Theriault and Tatton 1989). The ipsilateral terminations are then progressively eliminated until they reach the levels of the adult cat at about 2 months. Interestingly, evidence in humans more closely resembles the findings in the cat than macaque. In the new-born, focal TMS of the motor cortex elicits both contralateral and ipsilateral muscle contractions (Eyre et al. 2001). These responses have similar thresholds and amplitudes. The ipsilateral response has a shorter latency, indicative of the shorter length of the projection and in line with the expected latency of a direct pathway. Over the first two years of life the amplitude and frequency of the ipsilateral response decreases. Eyre and colleagues have suggested this resembles the pattern of ipsilateral pruning seen in the cat (Eyre et al. 2001; Lacroix et al. 2004; Palmer and Ashby 1992).

Ipsilateral pruning in the cat can be prevented by disruption to the motor cortex. During early development, the corticospinal pathways are dependent on cortical input to maintain their axons. If the activity of one side of the motor

cortex is silenced during postnatal weeks 3 to 7, the contralateral projections do not form terminations in many regions of the spinal cord (van Empelen et al. 2005). Instead, the ipsilateral pathways from the non-silenced hemisphere that are normally pruned are preserved. These ipsilateral projections terminate in both ventromedial areas of the intermediate zone (normally associated with axial muscle control) and lateral areas (associated with control of limb muscles) and persist into maturity.

Martin (2007) and Eyre (2004) have commented on the similarities with unilateral perinatal stroke in humans. Patients with unilateral perinatal stroke can be divided based on their response to TMS. The patients with strongest motor function of the contralesional hand and wrist have contralateral responses to TMS of the motor cortex (Benecke et al. 1991; Cincotta et al. 2000). Therefore, the more favourable outcome seems to depend on some preservation of descending pathways with contralateral projections (Lacroix et al. 2004). But the remaining patients can be separated again: those with relatively better hand function have fast conducting, high amplitude, ipsilateral responses that persist into adulthood (Carr 1996; Carr et al. 1993). This suggests that in some cases, when the crossed pathway from the lesioned cortex is non-functional, abnormal ipsilateral pathways from the non-lesioned hemisphere can provide some compensation for motor control of the hand contralateral to the lesion. Furthermore, those patients with better contralateral hand function are likely to have incurred brain damage before or around the time of birth. As with the kitten, this may indicate that there is an important period of development – possibly the period before and during corticospinal pruning – where the nervous system has greater potential for adaptation. Once this period has passed, prospects for recovery may worsen.

1.4.2 Pathways from the brainstem

In addition to corticospinal projections, human motor control is supported by a diverse set of pathways from nuclei in the brainstem, including rubrospinal, pontospinal, reticulospinal, vestibulospinal, tectospinal and interstitiospinal

tracts. Might these pathways provide additional routes for ipsilateral control, particularly of distal musculature? A long-held view of these pathways separates them into dorsolateral and ventromedial groups (Lawrence and Kuypers 1968a; Lemon 2008). The former terminates in the dorsolateral region of the intermediate zone of the spinal cord and controls the distal segments of the limbs. The latter terminates in the ventromedial area of the intermediate zone and provides postural control of head, neck, trunk and proximal limb movements.

The dorsolateral group includes the rubrospinal and pontospinal tracts. Rubrospinal neurones originate in the magnocellular red nucleus and, in the macaque monkey, receive cortical projections primarily from ipsilateral M1 (Colebatch and Gandevia 1989). As neurones from the magnocellular red nucleus descend they cross in the ventral tegmental decussation and, upon entering the spinal cord, are intermingled with corticospinal neurones in the dorsolateral funiculus. In man, however, only a very few terminate in the spinal cord and so can be accurately referred to as rubrospinal (Nathan and Smith 1982). These do not descend lower than the upper cervical segments. As with the pontospinal tract (arising in the ventrolateral pontine tegmentum), rubrospinal neurones terminate primarily in the contralateral dorsolateral intermediate zone, though there is evidence to suggest that some may have direct connections with motoneurones (Küchler et al. 2002; McCurdy et al. 1987). In cat and monkey, rubrospinal cells have been shown to drive contralateral forelimb and hindlimb muscles, preferentially activating distal and extensor muscles, although the contribution to any muscle activation is much smaller than that of corticospinal neurones (Belhaj-Saïf et al. 1998). Whilst the rubrospinal tract could potentially influence the control of hand and digit muscles, in humans it appears to be a small and exclusively crossed pathway. As such it does not seem to be a possible substrate of ipsilateral motor control.

In contrast to the dorsolateral group, the ventromedial group have bilateral projections. This group includes the vestibulospinal, tectospinal, interstitiospinal and reticulospinal tracts. Vestibulospinal neurones have their

origin in the lateral and medial vestibular nuclei. Alongside the semicircular canal and cerebellum, the vestibular nuclei also receive bilateral inputs from a variety of cortical areas (Fukushima 1997). Neurones from lateral vestibular nuclei descend within the lateral funiculus of the spinal cord (Nathan et al. 1996) before terminating in the ventromedial area. Projections from the medial vestibular nuclei descend within the medial longitudinal fasciculus. Reticulospinal neurones arise from the pontine and medullary portions of the reticular formation.

In the cat and monkey, the reticular formation receives bilateral cortical projections (Lawrence and Kuypers 1968b; Matsuyama and Drew 1997; Rho et al. 1997). Neurones from the pontine area descend on the ipsilateral side. They are distributed widely throughout the lateral, ventrolateral and ventral columns, but most densely within the medial longitudinal fasciculus (Nathan et al. 1996) and terminate in the ipsilateral ventromedial area. Projections from the medullary area travel along both the ipsilateral and contralateral dorsolateral funiculus terminating in the contralateral ventromedial area. In addition to these pathways, there are the tectospinal (primarily a crossed pathway arising from superior colliculus) and interstitiospinal tracts (an uncrossed pathway arising from the interstitial nucleus of Cajal). Both pathways also descend in the medial longitudinal fasciculus and have terminations in the ventromedial parts of the intermediate zone, though the size of the tectospinal tract is small (Harting 1977). Whilst these ventromedial pathways provide bilateral control of musculature, they are commonly thought to primarily influence axial and proximal musculature. For this reason, it is often assumed that – if any ipsilateral control of the hands and digits remains after brain injury – it cannot be attributed to these pathways.

1.4.3 Brainstem projections and hand function

These functional distinctions between the pathways do not appear to be absolute. This was evident as far back as Lawrence and Kuypers (1968a) studies of the macaque, where they inflicted bilateral corticospinal lesions. Six to ten hours later, the monkey's arms were flaccid, hanging loosely from

the shoulders. After 24 hours, they could grip the cage with their hands. Beyond 72 hours they could pick up pieces of food with their hands and gradually recovered strength. But even after five months they had not recovered the independent finger movement required to remove food from small holes. Lawrence and Kuypers concluded that this function is provided by the corticospinal tract. They then (1968b) interrupted the rubrospinal tract on one side. Shortly after the lesion the animals exhibited preserved axial and proximal function, but had considerable difficulty picking up food with the ipsilateral hand, indicating a role of the rubrospinal tract in whole-hand grasping. They animals could, however, use the hand to weakly cling to the cage bars. This indicates some control of hand muscles beyond that of the dorsolateral pathways, leaving the ventromedial pathways.

As discussed, the ventromedial pathways have many projections via the medial longitudinal fasciculus. In the macaque, motoneurones (Riddle et al. 2009) and interneurones (Riddle and Baker 2010) with projections to muscles for whole-hand grasping respond to microstimulation of neurones within the ipsilateral medial longitudinal fasciculus, with contraction of ipsilateral hand muscles. The medial longitudinal fasciculus contains neurones of the reticulospinal, vestibulospinal, tectospinal and interstitiospinal tracts (Nathan et al. 1996). Previous studies have only implicated the tectospinal and interstitiospinal tracts in postural, head and neck movements. The relative size of the reticulospinal and vestibulospinal tracts suggest they may be better candidates. Since these pathways receive bilateral inputs from the cortex, they also present potential paths for cortical control of ipsilateral hand muscles.

If the ventromedial pathways can support ipsilateral hand movement after disruption to the corticospinal system, motor control is likely to be qualitatively different (Baker 2011). Whilst corticospinal neurones diverge to a small number of motoneurones pools (Buys et al. 1986), reticulospinal axons branch to contact many different pools (Matsuyama and Drew 1997; Matsuyama et al. 1999). The likely consequence is greater co-activation of muscles and an absence of fractionated movement. Similarly, whilst

corticospinal neurones activate both flexor and extensor muscles, with a slight preference for the extensors (Cheney et al. 1991), reticulospinal neurones facilitate the flexors and inhibit extensors on the ipsilateral side and vice versa on the contralateral side (Davidson and Buford 2006; Davidson et al. 2007). These known physiological differences correspond with the impairments of patients with unilateral motor cortex damage, including hemispherectomised patients. These patients have difficulty with fractionated hand movement (Raghavan et al. 2006), involuntary activation of other muscles (Dewald et al. 1995) and an imbalance in flexor-extensor activation (Kamper et al. 2003). On the one hand, this supports the hypothesis that reticulospinal neurones could provide some input to the paretic hand after a unilateral lesion. On the other, it suggests that the quality of motor control that the reticulospinal projections could provide the hand is substantially poorer than the crossed corticospinal pathway.

1.4.4 Pre-surgical assessment

In summary, in healthy individuals motor control of the hand and wrists is primarily supported by the crossed corticospinal tract. The rubrospinal tract and ventromedial pathways may also make minor contributions, but the latter are more important for axial and proximal muscle control. However, since the ventromedial pathways have bilateral projections, their role may be important after a unilateral lesion to the motor cortex. On the other hand, ipsilateral corticospinal fibres – more numerous in the cat during early development – may also be present in humans. If injury occurs at a young enough age, pruning of the ipsilateral corticospinal pathways may be disrupted, providing a pathway for ipsilateral control from the contralesional cortex.

The extent of ipsilateral motor control (via either corticospinal pathways or relays in the brainstem) is assessed before hemispherectomy with functional magnetic resonance imaging (fMRI) and/or transcranial magnetic stimulation (TMS). Previous fMRI studies have shown that if, during either passive or active movement of the paretic hand, patients present with pre-surgical ipsilateral or bilateral activation of the cortex, hand function will be

unchanged or improved two years after surgery compared to pre-surgical levels (Carr 1996; Pilato et al. 2009).

Ipsilateral control can also be assessed with TMS. In a healthy adult, the delivery of a single, supra-threshold TMS pulse to the hand area of the motor cortex elicits a motor evoked potential (MEP) in the contralateral hand. The latency of the response indicates the signal is conducted along corticospinal neurones with monosynaptic connections to motoneurones (Rothwell 1991). In the case of a hemispherectomy candidate, if the paretic hand is receiving input from the ipsilateral cerebral hemisphere, then one expects an ipsilateral or bilateral response to TMS of the intact side (Carr 1996; Pilato et al. 2009; Sun et al. 2009).

Whilst these methods have been shown to be effective for pre-surgical planning, they have disadvantages. fMRI is costly, time-consuming and unsuitable for children who are very young or have severe behavioural problems. Furthermore, the fMRI signal is often too weak to provide conclusive evidence of ipsilateral control. TMS has the potential to elicit a seizure, is not available in all hospitals and may be an intimidating procedure for a child.

1.5 Remainder of the thesis

The remainder of this thesis will investigate these themes in further detail. The clinical histories of six hemispherectomised patients will be provided with recent structural MRI scans that reveal not only the dramatic disconnection or removal of a cerebral hemisphere, but also the effects of neuronal degeneration (Chapter 2). The extent of their disability and their capacity to perform a variety of functional tasks will be evaluated with standard clinical outcome measures. This will include motor tests, but also visual tests, since the processes of planning and controlling a movement are highly dependent on the visual representation of one's body and environment. The results of visual acuity, visual field and stereopsis testing will be presented. The motor tests in this chapter will include standard outcome measures and strength testing. The extensive disabilities of the upper limb contralateral to the

resected hemisphere will be demonstrated, though it will also be shown that, for this group of patients, certain tasks are still possible with the contralesional arm, in fact some can even perform functional tasks with their contralesional hand.

For this to be the case, the motor system in these patients must have adapted, allowing an unusual degree of ipsilateral motor control. The patients with better hand function also have mirror movements. This suggests that hand function might be associated with branching, descending motor pathways. Through time and frequency domain analysis of muscle recordings, it will be shown that those patients with relatively good hand function have common drive to the left and right hand muscles that travels along bilateral motor pathways (Chapter 3). The methods used in this chapter could be used to assess motor reorganisation in pre-surgical evaluation.

The motor performance of patients is currently assessed with clinical outcome measures. Kinematic assessment could complement these tests with objective measurements that can detect changes in specific parameters of motor control. Patients, along with a comparison group of healthy participants, will be tested on a novel reaching task (Chapter 4). Movement time, average and maximum speed, length index of the trajectory and number of movement units will be calculated for both arms. This is important because impairments could be present in both contralesional and ipsilesional arms. The statistical method that will be applied – mixed effects modelling – will provide a group analysis, but also evaluation of individual patient performance since – as confirmed by the clinical outcome – this is not a homogenous group.

The second theme of Chapter 4 is bimanual coordination. This will be investigated in terms of temporal inter-limb synchronisation and spatial inter-limb interference. Inter-limb synchronisation is a common property of bimanual movements. There is a strong tendency to lessen the speed of one arm so that the speed of the slower arm can be matched and the timing of movement onset and end can be synchronised. In children with unilateral

cerebral palsy, this tendency can break down. This section will ask if the same is true of hemispherectomised patients and, if so, what hypotheses can be advanced in respect to relationships between structure and function in the brain.

The chapter will then turn to bimanual coordination in the spatial domain. Just as the movement of one arm can influence the timing of the other, it can also influence the trajectory that the arm moves through in space. This can be seen when one tries to draw a circle with one hand and a square with the other, or tries to pat the head and rub the stomach simultaneously. These examples are artificial, but the limb trajectory of one arm may be influenced by the other during commonplace actions. This will be investigated by asking if the arm's trajectory during a bimanual act is statistically different to a unimanual act.

Spatial interference is believed to be caused by signals that are sent between the cerebral hemispheres, so what happens when all motor control is shifted to a single hemisphere? Do the reorganised cortical structures continue to communicate through an intra-cortical pathway? This question will be addressed by asking if spatial interference is also present in the reaching movements of hemispherectomised patients. As with inter-limb synchronisation, the results raise further interesting questions that could be addressed with functional neuroimaging. Finally, to ensure the results are not biased by factors such as visual impairment, reach distance, practice, fatigue or attention, the effects of blindfolding, target distance and trial number will be accounted for. The methods used in this thesis will be critically appraised, including the approach to participant recruitment, strategies for identifying important time points during the motion capture task and alternative methods of modelling the data.

Future directions will then be considered. This is the first study to provide movement analysis of a group of hemispherectomised patients. It could pave the way for this approach to be integrated into standard clinical assessment. A new method of pre-surgical assessment of motor reorganisation is

suggested here, using behavioural assessment and electrophysiological recordings. If adopted in clinical practice, this could avoid some of the difficulties associated with current techniques. The project also raises some important theoretical questions regarding the structure-function relationship in the hemispherectomised patient's remaining cerebral hemisphere. Future research could explore these questions in more depth.

2. Clinical assessments

AIM. To characterise long-term motor and visual outcomes after hemispherectomy in the context of clinical histories and a recent MRI scan.

METHOD. Six hemispherectomised patients were recruited (age 20-36 years; three male; five left-handed). Clinical histories were collated, a T1-weighted MRI scan was acquired and motor (dynamometry; Fugl-Meyer Assessment; Action Research Arm Test) and visual (field; acuity; stereopsis; thickness of retinal nerve fibre layer) tests were carried out.

RESULTS. Two out of six patients performed better on motor tests and had a history of relatively good contralesional upper limb function. Patients had greatest difficulty with hand/wrist movement, complex movement combinations and individual joint control. One patient had impaired ipsilesional fine motor ability. All patients had clear signs of Wallerian degeneration of the contralesional cerebral peduncle and ipsilesional cerebellar hemisphere. In addition to homonymous hemianopia, all patients had loss of the residual hemifield. Ranking of visual ability was not linked to ranking of motor ability.

INTERPRETATION. Hemispherectomised patients differ in terms of their outcomes, with some patients having a remarkable ability to use both hands with one cerebral hemisphere. In addition to contralesional motor deficits, some patients may also have ipsilesional deficits. Whilst all patients have a homonymous hemianopia after hemispherectomy, they may also have greater deficits in the ipsilesional than the contralesional eye.

2.1 Introduction

At pre-surgical baseline, candidates for hemispherectomy present with a range of motor problems (van Empelen et al. 2004; van Empelen et al. 2005) and most patients will have a homonymous hemianopia (Basheer et al. 2007; Devlin 2003; Koenraads et al. 2014; Moosa et al. 2013). Motor impairments include reduced strength, reduced range of motion, exaggerated reflexes and spasticity. Performance at functional tasks requiring the contralesional upper limb is often poor. Independence and involvement in social activities can be reduced.

Immediately after surgery, the contralesional limb is typically flaccid. In the long term the loss of cortical input has neuroanatomical consequences too, with degeneration of the contralesional cerebral peduncle and ipsilesional cerebellar hemisphere (Choi and Bastian 2007; Govindan et al. 2008; Mullin et al. 2015). Despite these effects, some strength may return to pre-operative levels. This is believed to be associated with the time of the initial lesion – patients with congenital rather than acquired lesions tend to have better outcomes (Bode et al. 2005; van der Kolk et al. 2012). It has been proposed that this is due to early lesions disrupting the pruning of ipsilateral corticospinal projections from the remaining hemisphere.

In contrast, all patients are expected to have homonymous hemianopia (Basheer et al. 2007; Devlin 2003; Koenraads et al. 2014; Moosa et al. 2013). Only one patient has been reported as having a residual contralesional visual field after hemispherectomy (Werth 2006) and the reliability of the methods used in this study has been questioned (Koenraads et al. 2014).

The aim of this chapter is to investigate these long-term effects in six hemispherectomised patients, documenting function, impairment and degeneration of neural structures.

2.2 Participants

Patients who had undergone hemispherectomy as treatment for intractable epilepsy were identified from the research records of the Cognitive Neuroscience and Neuropsychiatry Section of the UCL Institute of Child Health. 69 patients were identified from the research records. Patients were excluded if at the time of recruitment to the study they were: (1) younger than seven years of age; (2) lacked a complete medical history; (3) did not have English as their first language; (4) had undergone hemispherectomy less than six months prior.

Patients were also screened based on records of their motor ability. Patients were excluded from the study if either: (1) records indicated a dense hemiplegia or (2) no data was available on the function of the weaker hand/arm. The remaining thirteen patients were contacted by letter. Six patients agreed to take part (age range, 20–35 years; mean age, 29.2 years; three male; three female; five left-handed; one right-handed). These patients were then interviewed by telephone to determine if they had functional reach with the weaker arm, as required for the motion capture component of this thesis.

Participants were excluded from the MRI component of the study if the participant had claustrophobia, any trauma or surgery that may have left ferromagnetic material in the body, ferromagnetic implants or pacemakers, or an inability to lie still for the duration of the scan. One participant (H.W.) was excluded from the MRI component according to these criteria. All participants gave written informed consent. Experiments were conducted with local ethics approvals and in accordance with the Declaration of Helsinki.

Apart from the vision tests, all tasks used in this thesis (clinical outcome, neurophysiological and kinematic assessments) were completed within one visit over one or two days. Patients were given adequate time for breaks.

2.3 Methodology

2.3.1 Clinical histories

Clinical histories and neuropsychological test results were collated from case notes held within the Great Ormond Street Hospital and the Cognitive Neuroscience and Neuropsychiatry Section of the UCL Institute of Child Health. The neuropsychological tests that have been used have varied greatly between the patients in terms of type of assessment, frequency of administration (depending on the phase of investigation for each patient) and length of follow up. The information provided is not consistent for all patients, but aims to give as clearer overview of each patient's history as possible.

2.3.2 Motor tests

A research physiotherapist – Dr Linda Hammett – carried out the motor tests. These included the Fugl-Meyer Assessment, Action Research Arm Test (ARAT) and hand-held dynamometry of power grip and key pinch grip force. Normative values are provided in Appendix 1.

The physician and researcher Professor Axel R. Fugl-Meyer developed the Fugl-Meyer Assessment in 1975 for the evaluation of physical performance of the post-stroke hemiplegic patient (Fugl-Meyer et al. 1975). The assessment was designed to determine the stroke patient's stage of recovery. These stages had been proposed previously by the physical therapist Brunnstrom (1966): from flaccidity, to spasticity, to control of movement synergies, to mastering of movement patterns, to complex movement combinations, to individual joint control, to normal function. The upper limb section of the Fugl-Meyer assessment has 33 items, including reflex testing, movement observation, grasp testing and assessment of coordination. Each item is scored on an ordinal scale (0 = unable to perform; 1 = able to perform in part; 2 = able to perform) by the examiner. All upper limb motor components have been shown to be excellent in terms of inter-rater and intra-rater reliability (Platz et al. 2005; Yozbatiran et al. 2008) and, when tested on stroke patients, without floor effects (Lin et al. 2009). This assessment has been used in previous studies of hemispherectomised

patients (Bode et al. 2005; Bode et al. 2009; Choi et al. 2010; Liang et al. 2013).

The Action Research Arm Test (ARAT) was developed by Ronald C. Lyle (1981) for assessing recovery of upper limb function following cortical damage. Motor performance is tested on a range of functional tasks that involve grasp, grip, pinch and gross movement. Each item of the ARAT is scored on an ordinal scale, from 0 to 3. The test has been found to be excellent in terms of inter-rater and intra-rater reliability (Platz et al. 2005; Yozbatiran et al. 2008). Fourteen days after stroke, 41.5% of patients experienced floor effects, though by 180 days after stoke this had fallen to 11.3% (Lin et al. 2009).

Power grip and pinch grip strength can be measured with dynamometry. Inter-rater and intra-rater reliability have been found to be excellent (Boissy et al. 1999; Mathiowetz et al. 1984). This assessment has been used in previous studies of hemispherectomised patients (Dijkerman et al. 2008; Holloway et al. 2000). The procedure for hand-held dynamometry is for the participant to be seated with back, pelvis and knees as close as possible to a 90-degree angle. The shoulder should be abducted and neutrally rotated and the elbow flexed at 90-degrees. The forearm should be neutral, with the wrist held between 0-15 degrees of ulnar deviation. The arm should be unsupported and the dynamometer should be presented vertically and in line with the forearm. Each hand is tested three times, separately, and the maximum score is reported for each hand.

2.3.3 Visual tests

The Ophthalmology Department at Great Ormond Street Hospital carried out the tests of vision. Visual performance was tested, behaviourally, with three assessments: the logMAR chart, Goldmann Kinetic Perimetry and the Frisby Near Stereotest. In addition, the thickness of the retinal nerve fibre layer was measured with optical coherence tomography.

Visual acuity – the spatial resolution of the visual processing system – can be tested by asking a participant to identify letters on a printed chart from a set distance. The logMAR chart consists of rows of letters, with five letters per row, with letter sizes advancing in size from bottom to top in uniform steps on a logarithmic scale. The angle of resolution for the rows can range from 0.5 for the smallest letter to 20.0 for the largest letter. Visual acuity is scored with reference to the logarithm of the minimum angle of resolution. For example, a participant who can read up to 1.0 minute of visual angle will be given a score equal to the base-10 logarithm of 1, which is 0.00, if details can only be resolved up to 2 minutes of angle, they receive a score of $\log_{10}(2) = 0.30$, or at 0.50 visual angle they will receive a score of -0.30. A normal monocular acuity can be considered ≤ 0.100. Visual acuity can be poor if light rays are not properly refracted by the cornea and crystalline lens. To rule out this cause, a pinhole can be used to minimise incorrect refraction, permitting only unrefracted rays of light to reach the macula. The performance of the eyes can be compared by calculating the interocular difference in the logMAR scores. Visual acuity can be considered unequal if the difference is 0.100 or more. In the current test, visual acuity was tested both monocularly and with both eyes open with appropriate refractive correction using a logMAR chart placed at 4 meters.

The visual field – the portion of a person's surroundings that they can see at a moment in time – can be measured with Goldmann Kinetic Perimetry. A light is moved from different points in the periphery of vision to the centre until it is detected by the participant. Repeated testing establishes a boundary within which the participant can see, tested monocularly or binocularly. Visual field deficits can then be measured qualitatively using the modified Wall and George classification as Grade 0 (normal), Grade 1 (minimal loss), Grade 2 (mild loss), Grade 3 (moderate loss), Grade 4 (marked loss) or Grade 5 (blinding loss).

Stereopsis – the ability to determine relative depth through the use of binocular cues – can be measured with the Frisby Near Stereotest. Participants are presented with four random-pattern squares on a plate.

Using two eyes, a participant with normal stereoscopic binocular vision will additionally see a target – a circular shape – within one of the four random-pattern squares, lying in depth relative to its surround. If the participant views the squares with one eye, or if the participant lacks binocular stereopsis, the depth effect no longer obtains and the participant will not see the target. The depth effect occurs because the target and the surround are printed on opposite sides of the plate. The thinner the plate, then, or the steeper the angle that the plate is presented, the easier it is to discriminate the target. To evaluate the extent of the patient's disability, the tester presents plates of different thickness at varying angles, corresponding to different viewing angles up to 600". Patients are scored based on the viewing angle at which they can reliably perceive the target. Clinicians place scores into the following categories: [0, 40[" (normal), [40, 80[" (mild deficit), [80, 150[" (moderate deficit), [150, 600[" (marked deficit). If the participant cannot perceive the target at any of these angles, they are classified as having no stereopsis at near.

Finally, the thickness of the retinal nerve fibre layer (RNFL) can be estimated with optical coherence tomography (OCT). Images of the RNFL are captured with OCT and an algorithm can then calculate the area of the internal limiting membrane in microns.

2.4 Results

Results are summarised in Table 1.

2.4.1 Clinical history: C.B.

C.B. was born at term following a normal pregnancy. Weakness of the right side of the body was noticed at twelve weeks after birth and seizures began at the age of seven months. The aetiology of the seizures remains unknown. A left hemispherectomy (part removal and part disconnection of the left cerebral hemisphere) was performed for the relief of intractable epilepsy at the age of 12 years, 4 months. Further details regarding the anatomy of pre-surgical lesions and the surgical procedure are not provided in the case notes. Since the surgery C.B. has remained seizure-free.

C.B. was assessed pre-operatively, aged 11 years, 10 months. She achieved a Performance IQ of 46 and a Verbal IQ of 46 (exceptionally low range). Her basic reading abilities were at the level achieved by the average child aged 8 years and her reading comprehension abilities were at the level achieved by the average child aged 6 years, 6 months. Testing of power grip strength with a dynamometer revealed a severe weakness contralateral to the more affected cerebral hemisphere. It was reported that she did not exhibit mirror movements. She was unable to perform a peg-sorting task with her weaker hand. Peg-sorting assesses the patient's ability to grip small pegs with their fingers and place the pegs into slotted holes. Sensory testing was carried out on the fingers and the palm of the hand. Scores achieved on tests of stereognosis (0/16) and finger position sense (0/5) demonstrated severe sensory deficits in her weak hand compared to the strong hand.

The same methods of sensory testing and motor testing were repeated at nine weeks and again at four months after surgery. On both occasions, she scored zero on sensory testing of her weaker hand. She was unable to grip the dynamometer for strength testing of this hand and unable to lift pegs for a peg-sorting task. It was, however, reported that she retained some strength in this hand and could squeeze the experimenter's finger. As before, mirror movements were not present. She was seen again, post-operatively, aged 15

years, 11 months. She achieved a Verbal IQ of 62 and Performance IQ of 46 (both scores in the exceptionally low range). She was still unable to grip a dynamometer with her weaker hand, but it was again reported that she could squeeze the examiner's finger.

C.B. has previously taken part in a published study (Holloway et al. 2000), referred to as 'Patient 5'. She was reported to have no hand function and a moderate sensory impairment of the weaker upper limb. Electrical stimulation of the wrist elicited somatosensory evoked potentials in the remaining hemisphere.

At the time of the current assessment, C.B.'s age was 30 years, 1 month. She underwent all stages of behavioural testing and an MRI scan. From the MRI scan, it can be seen that C.B. has a smaller left cerebral peduncle and right cerebellar hemisphere (see Figure 3).

Figure 3. T1-Weighted MRI: C.B.

Note smaller left cerebral peduncle (see circle) and right cerebellar hemisphere (see square)

2.4.2 Clinical history: D.N.

D.N. was born with hemimegaencephaly, a rare neurological condition where one side of the brain is larger than the other. The right hemisphere was affected, being abnormally large. Weakness of the left side of the body was noticed and seizures began at the age of eight months. A right hemispherectomy was performed for the relief of intractable epilepsy at the age of 2 years, 8 months. Further details regarding the anatomy of pre-surgical lesions and the surgical procedure are not provided in the case notes.

D.N. was assessed pre-operatively, aged 1 year, 7 months, with the Bayley Scales of Infant Development. The Motor Scale component of the assessment does not account for hemiparesis/hemiplegia. If one limb is non-functional, the child may attempt to complete the test with the other limb only. Non-use of one limb can also make it difficult for the child to complete some items on the Mental Scale. According to this assessment D.N. was functioning at the age of a 12 – 13-month-old and had a short attention span. He could not yet walk, but could sit independently and had started crawling.

He was assessed post-operatively with the Bayley assessment at the age of 4 years, 5 months (1 year, 9 months after surgery), obtaining an age equivalent score on the Mental Scale of 15 months and on the Motor Scale of 19 months. He was re-tested at 5 years (2 years, 4 months after surgery) and obtained age equivalent scores of 22 months and 24 months on the Mental and Motor Scales, respectively. He was assessed on his cognitive abilities at age 11 years, 4 months and scored in the exceptionally low range, with a Verbal IQ of 56, a Performance IQ of 61 and Full Scale IQ of 53.

In addition to these standardised tests scores, case notes in D.N.'s file reported left hemiplegia, but significant amount of residual function. When asked, he could hold the researcher's hand with his hemiparetic hand. At the time of the current assessment, D.N.'s age was 23 years, 4 months. He underwent all stages of behavioural testing and had an MRI scan. From the

MRI scan it can be seen that D.N. has a smaller right cerebral peduncle and left cerebellar hemisphere (see Figure 4).

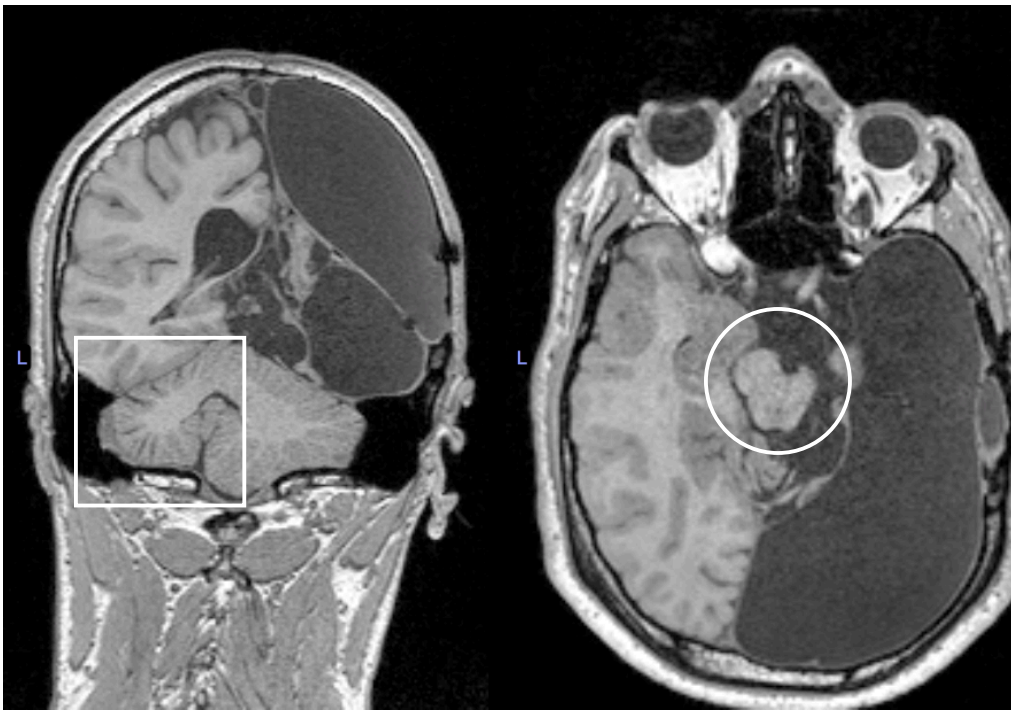

Figure 4. T1-weighted MRI: D.N.

Note smaller right cerebral peduncle (see circle) and left cerebellar hemisphere (see square).

2.4.3 Clinical history: E.B.

E.B. is believed to have suffered a pre or perinatal stroke of the left hemisphere. Weakness of the right side of the body was noticed aged five months and seizures began at the age of 18 months. These became regular at 3 years, 6 months. A left hemispherectomy (part removal, part disconnection) was performed for the relief of intractable epilepsy at the age of 13 years, 9 months. Further details regarding the anatomy of pre-surgical lesions and the surgical procedure are not provided in the case notes. Since surgery, she has remained largely seizure free (experiencing occasional 'absence' episodes, but no overt seizures), although she has been troubled by headaches and nausea.

E.B. was assessed pre-operatively, aged 12 years, 3 months. She achieved a Performance IQ of 60, a Verbal IQ of 49 and a Memory Quotient of 59 (all in the exceptionally low range). She had poor visuospatial skills (age equivalent 6 years on the Block Design and Object Assembly subtests of the Wechsler Scales of Intelligence), though as performance tests require motor coordination, her score may have been affected by her hemiparesis. Scores on tests of stereognosis (0/16) and finger position sense (0/5) demonstrated severe sensory deficits in her weaker hand. She could complete a tapping task with her weaker hand (1.5 taps per second), but with less speed than her stronger side (3.4 taps per second). During voluntary movement of either hand (fist rotation and finger opposition), pronounced mirror movements were reported as being present in the contralateral hand. It was reported that mirror movements had always been present.

She was assessed post-operatively, aged 15 years, 8 months (2 years, 10 months after surgery). She achieved a Performance IQ of 48, a Verbal IQ of 58 and a Full Scale IQ of 49 (all in the exceptionally low range). Scores of stereognosis (1/16) and finger position sense (0/5) remained very low. Unsurprisingly her tapping speed with her weaker hand (2.4 taps per second) was still lower than her stronger arm (4.1 taps per second), but for a hemispherectomised patient to be able to perform the task with the weaker

hand is itself unusual (Dijkerman et al. 2008). She was also able to participate in power grip dynamometer testing, scoring 21.5 kg with her stronger hand and 3 kg with her weaker hand. Mirror movements were reported as still very pronounced.

E.B. was assessed again, aged 17 years, 2 months. She achieved a Performance IQ of 66, a Verbal IQ of 70 and a Full Scale IQ of 67 – an improvement, but still in the exceptionally low range. She scored zero on testing of stereognosis (0/16) and finger position sense (0/5) of her hemiparetic hand. The tapping score for her weaker hand was 3.0 taps per second and stronger hand was 3.7. Her power grip dynamometer score for her stronger hand was 21.7 kg with her stronger hand and 3.5 kg with her weaker hand. Mirror movements were still pronounced. E.B. was re-tested, aged 18 years, 5 months. She achieved a Performance IQ of 64, a Verbal IQ of 70 and a Scale IQ of 66. Her stereognosis (0/16) was still zero. The tapping score for her weaker hand was 2.9 taps per second and for her stronger hand it was 3.7. Her power grip dynamometer score for her stronger hand was 23.7 kg with her stronger hand and 4.8 kg with her weaker hand.

E.B. has previously taken part in a published study (Holloway et al. 2000), referred to as ‘Patient 6’. She was reported to have a moderate deficit in hand function and severe deficit in sensory function of the weaker upper limb. Motor reorganisation could not be detected with fMRI during passive hand movement. Mirror movements were reported as present. Electrical stimulation of the hemiparetic wrist elicited somatosensory evoked potentials in the remaining hemisphere.

At the time of the current assessment, E.B.’s age was 34 years, 11 months. She underwent all stages of behavioural testing and an MRI scan. From the MRI scan it can be seen that E.B. has a smaller left cerebral peduncle and right cerebellar hemisphere (see Figure 5).

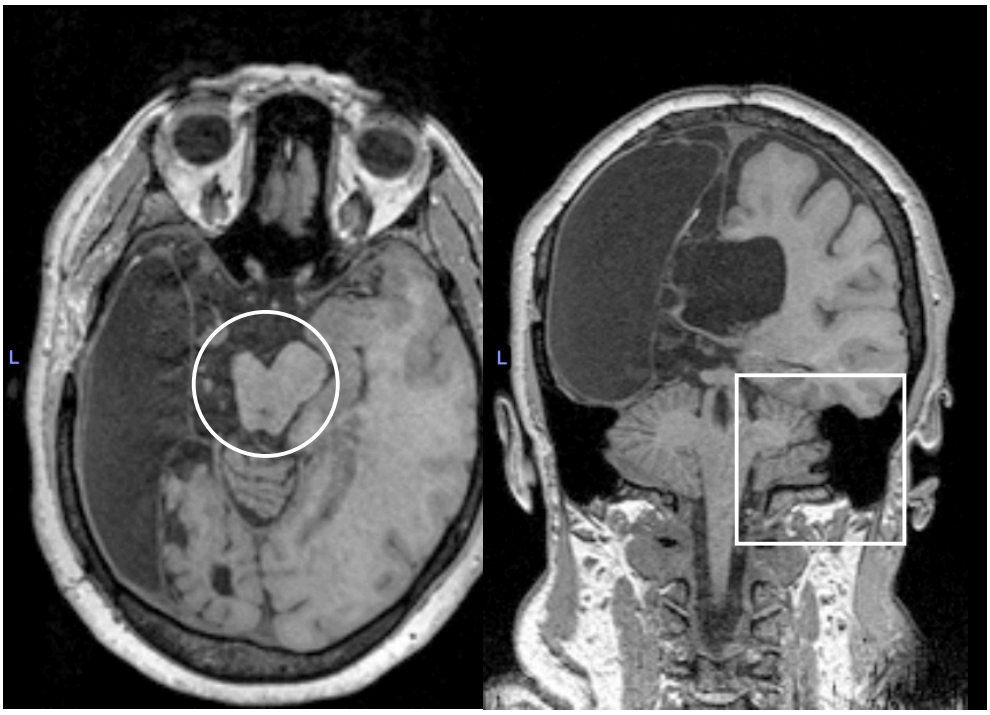

Figure 5. T1-weighted MRI: E.B.

Note smaller left cerebral peduncle (see circle) and right cerebellar hemisphere (see square).

2.4.4 Clinical history: H.W.

H.W. was born one of twins. The other infant was stillborn having died in utero probably two weeks before delivery. Weakness of the right side of the body was noticed at six months after birth. Seizures began at the age of seven years. Electroencephalography (EEG) recordings showed bilateral abnormalities with frequent epileptiform discharges over the left hemisphere. The activity was grossly asymmetrical, with both normal and abnormal activity reduced on the left. A CT scan performed at the same time showed marked left hemi-atrophy with almost all of the cortical mantle destroyed, except for a small remnant in the frontal region. A total left hemispherectomy was performed for the relief of intractable epilepsy at the age of 9 years, 10 months. Further details regarding the surgical procedure are not provided in the case notes.

Neuropathological examination of the removed hemisphere showed it to be very small. Cortical grey matter was better preserved in the frontal region. Sulci of the temporal and occipital regions showed cortical thinning with almost complete absence in the depths of some sulci. The changes were more marked in the upper half of the hemisphere and in the occipital region. Several gyri contained large cysts and cavities were also present in the underlying white matter. The hippocampus was well preserved but showed moderate astrocytosis in the endofolium. The appearance suggested circulatory damage at a late stage in prenatal life or in the perinatal phase. Since the surgery H.W. has remained seizure-free.

No pre-operative assessments of function are on record. She was assessed post-operatively, aged 10 years, 11 months. She achieved a Performance IQ of 87 (low average range), a Verbal IQ of 94 (average range) and a Full Scale IQ of 89 (low average). Her Memory Quotient (100) was consistent with her Verbal IQ. Visual field testing revealed homonymous hemianopia, as is usual in hemispherectomised patients. She had intermittent squint in the left eye. There was no evidence of dysfunction in the intact hemifields for colour, in either eye. Acuity was normal in both eyes. Scores of stereognosis

(3/16) and finger position sense (2/5) demonstrated severe sensory deficits in her weaker hand, but some ability. When performing a tapping task, with her stronger hand she scored 5.2 taps per second and with her weaker hand she scored 2.9 taps per second. Dynamometry power-grip testing also found her stronger hand to be within the normal range at 30.1 kg. With her weaker hand she produced 12.3 kg of force. She could wiggle her fingers and perform thumb to index finger opposition. The examiner noted the presence of mirror movements when attempting to wiggle the fingers of one hand. It was not noted if mirror movements in the contralateral hand were more pronounced during voluntary movement of her weaker hand or her stronger hand.

She was tested again aged 18 years, 5 months. Scores of stereognosis (0/16) and finger position sense (0/5) of her hemiparetic hand were now at zero. The tapping speed of her stronger hand was 5.1 taps per second, whilst for her weaker hand it was 2.7. Dynamometer testing found she could produce 26 kg of force with her stronger hand and 10.7 kg of force with her weaker hand.

H.W. has previously taken part in a published study (Dijkerman et al. 2008). Of the twelve patients studied by Dijkerman et al. she was the only patient who could use the power-grip dynamometer with her weaker hand, producing 33.3% of the average force of matched controls. She was one of only two patients who could tap from her weaker forearm, achieving a score that corresponded to 45.5% of the average of matched controls. She also demonstrated impaired passive joint movement sense, pressure sensitivity, sensitivity to hot and cold and awareness of double simultaneous stimulation on her weaker side.

At the time of the current assessment, H.W.’s age was 36 years, 5 months. She underwent all stages of behavioural testing but was excluded from the MRI scan due to ferromagnetic implants.

2.4.5 Clinical history: J.S.

J.S. was born at term following a normal pregnancy. He was diagnosed with Goldenhar syndrome soon after birth due to the malformation of his right ear. Weakness of the right side of the body was noticed at nine months after birth. Seizures began at the age of 12 years. An MRI scan was conducted and he was found to have a mature lesion in his left hemisphere due to middle cerebral artery (MCA) infarction and left sided atrophy. His EEG showed left-sided epileptiform activity interictally and generally slow activity over the left hemisphere. A left hemispherectomy (part removal and part disconnection of the left cerebral hemisphere) was performed for the relief of intractable epilepsy at the age of 15 years. Further details regarding the anatomy of pre-surgical lesions and the surgical procedure are not provided in the case notes. Since the surgery J.S. has remained seizure-free.

J.S. was seen for pre-surgical evaluation aged 14 years, 2 months. His perceptual reasoning was relatively high (14^{th} percentile), compared to his lower scores for verbal comprehension (1^{st} percentile), working memory (1^{st} percentile) and processing speed (2^{nd} percentile). He was seen again post-operatively at the age of 16 years. His perceptual reasoning remained high (14^{th} percentile), showed some improvement in verbal comprehension (4^{th} percentile), working memory (2^{nd} percentile) and processing speed (5^{th} percentile). At the age of sixteen he was reported to be receiving weekly occupational therapy and physiotherapy at school every week.

J.S. recently participated in an unpublished study of his language abilities. Researchers from the language study recommended J.S. for this study based on his residual arm function. At the time of the current assessment, J.S.'s age was 20 years, 10 months. He underwent all stages of behavioural testing except for dynamometry testing of his stronger hand. He also underwent an MRI scan. From the MRI scan it can be seen that J.S. has a smaller left cerebral peduncle and right cerebellar hemisphere (see Figure 6).

Figure 6. T1-weighted MRI: J.S.

Note smaller left cerebral peduncle (see circle) and right cerebellar hemisphere (see square).

2.4.6 Clinical history: P.O.

P.O. was born with Sturge-Weber Syndrome. Sturge-Weber Syndrome is a congenital disorder characterised by a facial birthmark (often referred to as a 'port-wine stain') and neurological abnormalities that normally only affect one side of the brain. P.O. was born with such a facial birthmark and, six days after birth had his first seizure. A CT scan showed a normal ventricular system but widening of the sulci in the left posterior parietal region, indicative of left hemiatrophy.

At the age of six months he was showing signs of weakness of the right side of his body. By seven months it was apparent that he had right hemianopia. As a baby, he did not babble or gurgle much and by the age of 33 months he was yet to develop speech. Over the following years he had behavioural problems, showed serious developmental delay and remained speechless.

At the age of 7 years, 7 months, MRI and CT scans revealed an atrophic and diffusively calcified left hemisphere and an enlarged right hemisphere. A left hemispherectomy (full removal of the left cerebral hemisphere by the modified Adams technique) was performed at the age of 8 years, 6 months. The bone was filled with large venous channels and the dura was thickened due to infliltration by numerous small arterioles. The pia and arachnoid had also been infiltrated by abnormal blood vessels. The hemisphere was dusky blue in appearance and firmer than normal due to difuse calcification. After the removal, the foramen of Monro was plugged with muscle to prevent blood within the subdural cavity from irrigating the ventricular system and the dural flap was sutured to both the tentorium and the dura lining the anterior and middle cranial fossae to minimise the volume and the surface area of the subdural cavity.

Since surgery he has remained seizure-free. One month after withdrawal of his anticonvulsant medicine, at the age of 9 years, 4 months, he began speaking. The progression of his abilities has been documented in a case study (Vargha-Khadem et al. 1997). The following details were reported within that study.

Before surgery, in addition to profound weakness, P.O. had hemiatrophy, increased tone and hyperreflexia on the right side of his body, especially the upper limb. He still could use his right side for some functional tasks, such as holding a cup or catching a ball with both hands. Post-operative neurological assessment at age 11 years, 10 months found a 3 cm shortening of his right arm. Independent movement of his right fingers was not possible, but he could grasp objects between thumb and fingers. Dynamometer power-grip testing at 11 years, 3 months found he could produce 19.7 kg force with his stronger hand and 2.7 kg with his weaker hand. Tests of tapping speed found his stronger arm (3.9 taps per second) to be 1 SD below the sex-matched, age-equivalent mean, whilst his weaker arm (1.6 taps per second) was far slower. Mirror movements were reported as not being present. Motor reorganisation was assessed with TMS. Stimulation of the remaining hemisphere of the motor cortex elicited a bilateral muscle response. The response on the weaker side was smaller and of longer latency. Electromyography (EMG) recordings were taken from hand muscles during a bilateral voluntary contraction. No correlation was found between the left and right signals, suggesting that common, bilateral drive to the hand musculature was not present or was too small to be detected.

P.O. has also taken part in another published study (Holloway et al. 2000), where he was referred to as Patient 1. He was reported to have severe deficits in motor and sensory function of the weaker upper limb. Motor reorganisation could not be detected with fMRI during passive hand movement. Mirror movements were absent. Both electrical stimulation of the wrist and vibrational stimulation of the fingers elicited somatosensory evoked potentials in the remaining hemisphere.

At the time of the current assessment, P.O.'s age was 33 years, 5 months. He underwent all stages of behavioural testing and an MRI scan. From the MRI scan it can be seen that P.O. has a smaller left cerebral peduncle and right cerebellar hemisphere (see Figure 7),

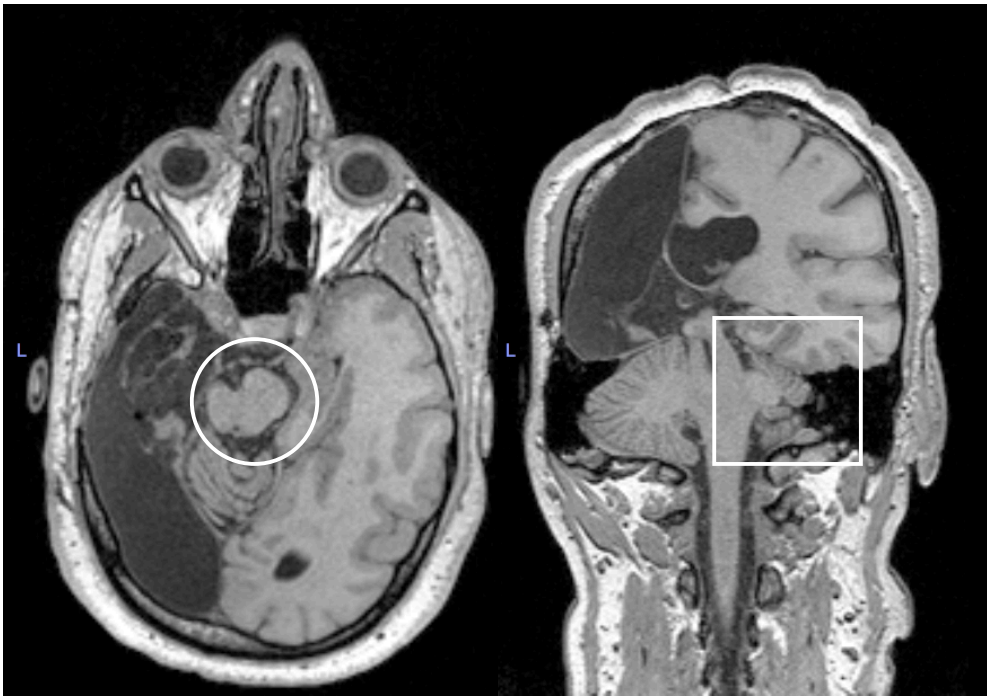

Figure 7. T1-weighted MRI: P.O.

Note smaller left cerebral peduncle (see circle) and right cerebellar hemisphere (see square).

2.4.7 Motor tests

By total upper limb score on the Fugl-Meyer Assessment the patients were ranked, in descending order: E.B., H.W., D.N., P.O., J.S. and C.B. (see Table 2). Mean scores were lowest for tasks involving the wrist (*M* = 0.47, *SD* = 0.63), followed by hand (*M* = 0.81, *SD* = 0.59). C.B. could not perform any of the wrist tasks. Mean scores for movements involving the shoulder, elbow and forearm were ranked, in descending order: volitional extensor movements within synergy (*M* = 1.72, *SD* = 0.46), volitional flexor within synergy (*M* = 1.47, *SD* = 0.65), reflex activity (*M* = 1.25, *SD* = 0.87), volitional movements little/no synergy dependence (*M* = 1.00, *SD* = 0.69) and volitional movement mixing flexor and extensors (*M* = 0.94, *SD* = 0.42).

By total score of the weaker upper limb on the Action Research Arm Test the patients were ranked, in descending order: E.B., H.W., P.O., D.N., J.S. and C.B. (see Table 3). All patients scored full marks (57/57) for the stronger upper limb, except for C.B. who scored 49/57. C.B. scored full marks for all tests except for those requiring pinch grip (see Table 4). Mean ARAT scores for the weaker upper limb were ranked, in descending order: gross movement (*M* = 2.11, *SD* = 0.32), grasp (*M* = 1.58, *SD* = 1.00), power grip (*M* = 1.46, *SD* = 1.10) and pinch grip (*M* = 0.22, *SD* = 0.59). Two patients (E.B. and H.W.) had better function than the others and could lift objects with their contralesional hand, such as a small piece of wood, a glass and a marble.

Dynamometry scores for the stronger hand of J.S. were not taken and are labelled as missing data. With the weaker hand, J.S. and C.B. were unable to produce any power grip force. The remaining patients (H.W., E.B., D.N. and P.O.) were all able to produce a small amount of power grip force. The only patient that could produce any key pinch grip force with the weaker arm was H.W. and output was very low.

2.4.8 Visual tests

J.S. was the only participant with visual acuity of either eye within the normal range of -0.20 to 0.00. The only participants with visual acuity that was equal between the eyes were J.S. and H.W., with an interocular difference below 0.100. All other patients had better visual acuity in the eye ipsilateral to the side of surgery. For the eye contralateral to the side of surgery, the patients were ranked from best to worst: J.S. (-0.04), H.W. (0.04), P.O. (0.40), D.N. (0.44), C.B. (0.70) and E.B. (0.72). For the eye ipsilateral to the side of surgery, the patients were ranked from best to worst: J.S. (-0.04), D.N. (0.04), H.W. (0.06), C.B. (0.06), P.O. (0.10) and E.B. (0.30).

Given the loss of the occipital cortex on one side, all participants were expected to have homonymous hemianopia contralateral to the side of surgery and this was confirmed, however there was constriction of the peripheral residual field. This loss was minimal or mild for two patients (J.S. and D.N.), moderate for two patients (H.W. and P.O.) and marked or blinding for two patients (C.B. and E.B.). Where there was a difference between the eyes, there was greater loss of the residual visual field in the eye contralateral to the side of surgery.

When tested for depth perception, all participants could discriminate the target, showing stereopsis at near, except C.B., who could not perceive the target under any of the conditions. The patients were ranked from best to worst: J.S. (55”, mild deficit), H.W. (85”, moderate deficit), D.N. (110”, moderate deficit), P.O. (110”, moderate deficit), E.B. (600”, marked deficit) and C.B. (no stereopsis at near).

For every patient, the global retinal nerve fibre layer was smaller in the eye contralateral to the operated hemisphere compared to the ipsilateral eye. This was on average reduced by 14.5% (range 8.9-19.8%) in the contralateral eye compared to the ipsilateral eye. The patients were ranked in terms of retinal nerve fibre layer of the contralateral eye, from high to low (in microns): J.S. (82), D.N. (81), P.O. (69), E.B. (62), H.W. (58) and C.B. (45).

For the ipsilateral eye the ranking was: D.N. (101), J.S. (90), P.O. (86), E.B. (74), H.W. (66) and C.B. (50).

Table 1. Summary of motor and visual tests

HM = Hemimegencephaly; SWS = Sturge-Weber Syndrome

	C.B.	*D.N.*	*E.B.*	*H.W.*	*J.S.*	*P.O.*
Sex	Female	Male	Female	Female	Male	Male
Side of hemispherectomy	Left	Right	Left	Left	Left	Left
Aetiology	Unknown	HME	Stroke	Stroke	Stroke	SWS
Age at onset of hemiparesis	0y, 3m	Unknown	0y, 5m	0y, 6m	0y, 9m	0y, 6m
Age at first seizure	0y, 7m	0y, 8m	1y, 6m	7y, 0m	12y, 0m	0y, 1m
Age at time of surgery	12y, 4m	2y, 8m	13y, 9m	9y, 10m	15y, 0m	8y, 6m
Time since surgery	17y, 9m	20y, 8m	21y, 2m	26y, 7m	5y, 10m	24y, 11m
Power grip (contralesional, kg)	0	5	2	7	0	5
Power grip (ipsilesional, kg)	14	35	23	28	*Missing data*	29
Pinch grip (contralesional, kg)	0	0	0	1	0	0
Pinch grip (ipsilesional, kg)	2.5	5	8	12	*Missing data*	7
Visual acuity: contralesional eye	0.70	0.44	0.72	0.04	-0.04	0.40
Visual acuity: ipsilesional eye	0.06	0.04	0.30	0.06	-0.04	0.10
Visual field: contralesional eye	5	2	5	3	2	3
Visual field: ipsilesional eye	4	1	4	3	1	3
Near stereopsis (seconds of arc)	No stereopsis	110”	600”	85”	55”	110”
RNFL: contralesional eye	45	81	62	58	82	69
RNFL: ipsilesional eye	50	101	74	66	90	86

Table 2. Results of Fugl-Meyer Assessment

M = mean; SD = standard deviation

			CB	*DN*	*EB*	*HW*	*JS*	*PO*	**M**	**SD**
Shoulder / elbow / forearm	Reflex activity									
		Flexors (biceps; finger flexors)	2	2	2	1	2	2	1.25	0.87
		Extensors (triceps)	2	0	1	1	0	0		
	Flexor – volitional movement within synergy									
		Shoulder retraction	1	2	2	1	2	2	1.47	0.65
		Shoulder elevation	1	2	2	1	1	2		
		Shoulder abduction	1	2	2	2	2	2		
		Shoulder external rotation	1	1	2	1	1	2		
		Elbow flexion	2	2	2	2	2	2		
		Forearm supination	0	0	1	0	1	1		
	Extensor – volitional movement within synergy									
		Shoulder adduction	2	2	2	2	2	2	1.72	0.46
		Elbow extension	1	1	1	1	1	2		
		Forearm pronation	2	2	2	2	2	2		
	Volitional movement mixing flexor and extensor									
		Hand on lumbar spine	1	1	1	1	1	1	0.94	0.42
		Shoulder flexion	1	2	1	1	1	1		
		Forearm pronation / supination	0	1	1	1	1	0		
	Volitional movements, little/no synergy dependence									
		Shoulder abduction	1	2	2	1	2	1	1.00	0.69
		Shoulder flexion	1	2	1	1	1	1		
		Forearm pronation-supination	0	0	0	1	1	0		
Wrist	Wrist stability – elbow 90°		0	0	1	2	0	0	0.47	0.63
	Wrist flexion/extension – elbow 90°		0	1	1	1	0	1		
	Wrist stability – elbow 0°		0	0	1	2	0	0		
	Wrist flexion/extension – elbow 0°		0	0	1	1	0	1		
	Circumduction		0	0	0	1	0	0		
Hand	Mass flexion		1	1	2	2	1	1	0.81	0.59
	Mass extension		0	1	2	2	1	1		
	Grasp A – distal finger grasp		1	1	1	1	0	1		
	Grasp B – thumb adduction grasp		1	1	1	0	1	0		
	Grasp C – thumb to index finger		1	0	1	0	1	0		
	Grasp D – cylinder grasp		0	1	1	1	0	1		
	Grasp E – spherical grasp		0	1	0	1	1	0		
Other	Tremor		2	2	2	2	2	2	1.50	0.51
	Dysmetria		1	1	1	1	2	2		
	Speed		1	2	1	1	1	1		
Total (out of 66)			**28**	**36**	**41**	**38**	**33**	**34**	**35**	**4.47**

Table 3. Results of Action Research Arm Test, contralesional arm

M = mean; SD = standard deviation

		CB	*DN*	*EB*	*HW*	*JS*	*PO*	**M**	**SD**
Grasp (to shelf)									
	Pick up a 10cm cube of wood	0	0	2	2	0	2	1.58	1.00
	Pick up a 2.5cm cube of wood	0	2	3	2	2	2		
	Pick up a 5cm cube of wood	0	2	3	2	2	2		
	Pick up a 7.5cm cube of wood	0	2	3	2	0	2		
	Cricket ball 7.5cm	0	2	3	2	2	2		
	Sharpening stone 10 x 2.5 x 1cm	0	2	1	2	2	2		
Grip (on table)									
	Pour water from glass to glass	0	0	2	1	1	1	1.46	1.10
	Move tube 2.25cm across table	0	2	3	3	2	1		
	Move tube 1cm x 16cm	0	2	3	3	2	2		
	Put washer over bolt	0	1	1	3	0	2		
Pinch (to shelf)									
	Ball bearing between ring finger and thumb	0	0	0	0	0	0	0.22	0.59
	Marble between index finger and thumb	2	0	2	2	0	1		
	Ball bearing held between middle finger and thumb	0	0	0	0	0	0		
	Ball bearing held between index finger and thumb	0	0	0	0	0	0		
	Marble held between ring finger and thumb	0	0	1	0	0	0		
	Marble held between middle finger and thumb	0	0	0	0	0	0		
Gross movement									
	Place hand behind head	2	2	2	2	2	3	2.11	0.32
	Place hand on top of head	2	2	2	2	2	2		
	Hand to mouth	2	2	3	2	2	2		
Total contralesional arm (out of 66)		8	21	34	30	19	26	23	9.21

Table 4. Results of Action Research Arm Test, ipsilesional arm

M = mean; SD = standard deviation

		CB	*DN*	*EB*	*HW*	*JS*	*PO*	**M**	**SD**
Grasp (to shelf)									
	Pick up a 10cm cube of wood	3	3	3	3	3	3	3.00	0.00
	Pick up a 2.5cm cube of wood	3	3	3	3	3	3		
	Pick up a 5cm cube of wood	3	3	3	3	3	3		
	Pick up a 7.5cm cube of wood	3	3	3	3	3	3		
	Cricket ball 7.5cm	3	3	3	3	3	3		
	Sharpening stone 10 x 2.5 x 1cm	3	3	3	3	3	3		
Grip (on table)									
	Pour water from glass to glass	3	3	3	3	3	3	3.00	0.00
	Move tube 2.25cm across table	3	3	3	3	3	3		
	Move tube 1cm x 16cm	3	3	3	3	3	3		
	Put washer over bolt	3	3	3	3	3	3		
Pinch (to shelf)									
	Ball bearing between ring finger and thumb	1	3	3	3	3	3	2.78	0.64
	Marble between index finger and thumb	3	3	3	3	3	3		
	Ball bearing held between middle finger and thumb	1	3	3	3	3	3		
	Ball bearing held between index finger and thumb	3	3	3	3	3	3		
	Marble held between ring finger and thumb	1	3	3	3	3	3		
	Marble held between middle finger and thumb	1	3	3	3	3	3		
Gross movement									
	Place hand behind head	3	3	3	3	3	3	3.00	0.00
	Place hand on top of head	3	3	3	3	3	3		
	Hand to mouth	3	3	3	3	3	3		
Total ipsilesional arm (out of 66)		49	57	57	57	57	57	55.7	3.27

2.5 Discussion

2.5.1 Clinical histories

As expected, all patients investigated here have severe hemiparesis. Where reported, this was noted in the first year of life. The aetiology of the patients' seizures varied, though, including stroke, hemimegaencephaly and Sturge-Weber syndrome. Age at onset of seizures ranged from 1 month after birth to 12 years. Age of surgery ranged from 2 years, 8 months to 15 years. Three of the six cases particularly stand out: E.B., H.W. and P.O. On post-operative testing, each of these patients could complete both tapping and dynamometry tasks with the hand contralateral to the operated hemisphere. Post-operatively, mirror movements were reported as present in both E.B. and H.W., and were also noted pre-operatively in E.B. (there are no notes on pre-operative assessment of H.W.). The case notes of C.B. and P.O. report mirror movements as not being present. C.B. was noted to have particularly poor motor function, but some minimal strength in her weaker hand. There was very little information available on the sensory and/or motor function of D.N. and J.S.

2.5.2 MRI scans

Recent T1-weighted MRI scans were acquired for all patients except H.W. These demonstrate that, for all participants, the size of the cerebral peduncle ipsilateral to the resected hemisphere is visibly smaller than the opposite cerebral peduncle, and the size of the contralateral cerebellar hemisphere is visibly smaller than the opposite cerebellar hemisphere. The cerebral peduncles contain fibres that carry information from the ipsilateral cortex to the contralateral spinal cord (corticospinal tract), the pontine nuclei en route to the contralateral cerebellar hemisphere (corticopontine tract) and the nuclei of the cranial nerves (corticobulbar tract). Damage to the cerebral cortex can starve these axons of their input, leading to Wallerian degeneration of connected pathways and deafferentation of connected structures, such as the contralateral cerebellar hemisphere. This in turn leads to crossed cerebellar diaschisis (depression of blood flow and metabolism).

These effects have been demonstrated in previous studies of hemispherectomised patients (Choi and Bastian 2007; Govindan et al. 2008; Mullin et al. 2015).

2.5.3 Motor performance

The Fugl-Meyer and Action Research Arm Test for the weaker arm were in broad agreement in terms of ranking: by both measures E.B. and H.W. were the least impaired, P.O. and D.N. were ranked in the middle and J.S. and C.B. were the most impaired. As predicted by the theory on which the Fugl-Meyer Assessment was based (Fugl-Meyer et al. 1975), patients had greatest difficulty on those tests that required complex movement combinations or individual joint control. All patients had greatest difficulty on the Action Research Arm Test with tasks involving the hand and wrist of the weaker upper limb. What was perhaps surprising was that wrist movement was often more impaired than hand movement. Notes by the research physiotherapist suggest this may be due to impaired range of movement.

All patients could perform gross movement tasks, such as placing the weaker hand behind the head. This makes sense in terms of the neuroanatomy of the motor system, as proximal musculature receives bilateral connections from the motor cortex and so would logically be less affected by unilateral brain damage. This is supported by previous research (Dijkerman et al. 2008). Patients had extreme difficulty with tasks that involved pinch grip, presumably due to severe weakness in the intrinsic hand muscles. But, whilst C.B. could only perform one whole hand grip/grasp task, all other patients could perform many types. This level of hand function is unusual after hemispherectomy (Holloway et al. 2000), though patients were excluded if they did not have functional reach with the weaker arm. This requirement was necessary to ensure that all participants could perform the motion capture task of this thesis, but will have resulted in the exclusion of patients with poorer motor function.

It has been shown before that patients can have deficits in force production with the stronger upper limb after hemispherectomy. Whilst significant

strength impairments have been found for proximal but not distal musculature, dexterity was found to be impaired for the index finger and forearm (Dijkerman et al. 2008). A study of adult stroke patients also found strength impairments for proximal but not distal muscle groups (Colebatch and Gandevia 1989). It has been proposed that proximal muscles are more likely to be affected, since they have more bilateral connections with the cortex – hence damage to one hemisphere should affect the proximal muscles of both arms (Lawrence and Kuypers 1968b). In the current study, only one patient (C.B.) exhibited impairments in the stronger upper limb and only for fine motor tasks. Whilst this conflicts with previous studies of strength testing, it does agree with Dijkerman et al.'s assessment of dexterity.

2.5.4 Visual performance

There were large differences in the visual performance of the patients. In the contralesional eye, J.S. has normal visual acuity and the highest RNFL thickness of the patients tested here. He has homonymous hemianopia, as expected, but the loss of vision in the residual hemifield of this eye is mild. In his ipsilateral eye, he also has normal visual acuity, relatively high RNFL thickness and minimal loss of vision in his residual hemifield. His eyes have equal visual acuity and he has a mild deficit of stereopsis at near. In contrast, C.B. and E.B. have extremely impaired vision. C.B. has very poor visual acuity in the contralateral eye, E.B. has similarly poor visual acuity in both eyes and both patients have homonymous hemianopia alongside marked or blinding loss of the residual visual field in both eyes and marked or total loss of stereopsis at near. The ranking of patients was similar for all tests, with J.S. performing the best, D.N., P.O. and H.W. ranked in the middle and E.B. and C.B. scoring the poorest.

It was interesting to note that all patients had loss of the residual hemifield and there appeared to be degeneration of the RNFL. A simple theoretical assumption might be that vision would only be affected for the hemifield contralateral to the resected hemisphere, corresponding to the loss of

occipital cortex. The cause of this additional loss would be an interesting topic for further investigation.

2.5.5 Conclusions

This chapter has documented a range of outcomes of hemispherectomy. Homonymous hemianopia appears to be an inevitable consequence, but the visual acuity and loss of vision in the remaining hemifield varies. Similarly, some patients can retain a remarkable level of functional ability with the contralesional hand, with enough capacity to grasp and lift small objects. As with the loss of vision in the ipsilesional hemifield, patients may also have a loss of functional ability in the ipsilesional hand for fine motor tasks. Though, whilst one should be careful about making generalisations with this small sample size, the evidence here does not suggest any relationship between residual visual and motor function, since there was no match in the ranking of these functions.

3. Neurophysiological assessment of motor pathways

AIM. To test the hypothesis that patients with superior upper limb function after hemispherectomy have a common pathway to the left and right distal upper limb muscles, demonstrated by intense persistent mirror movements of the hands and fingers and shared physiological drive to the left and right upper limb motoneurone pools.

METHOD. Six hemispherectomised patients were recruited (age 20-36 years; three male; five left-handed). Surface EMG was recorded from left and right wrists during voluntary activity and these recordings were subjected to time and frequency domain analysis. The results were compared to those of twelve typically developed controls matched for age and sex (age 19-37 years; six male; one left-handed).

RESULTS. Those hemispherectomised patients with good upper limb motor outcome (demonstrated by higher scores on upper limb testing) presented with intense mirror movements and synchronised left and right motoneurone activity.

INTERPRETATION. The results sugges that superior hand function post-surgery is associated with the presence of a common pathway to left and right hand muscles.

3.1 Introduction

In the preceding chapter it was shown that, after hemispherectomy, some patients retain some functional use of the hand that is contralateral to the operated hemisphere. From the cases presented in this thesis, E.B. and H.W. performed particularly well – total combined scores for wrist and hand tasks on the Fugl-Meyer Assessment were 12 and 14 out of 24, respectively, compared to an average of 8 for the entire patient group. But in the previous chapter it was said that, in the healthy adult, hand muscles are driven almost entirely by corticospinal neurones that originate in the contralateral cerebral hemisphere. For this reason, one would expect a total or almost total loss of contralateral hand function. For hand function to persist these patients must have abnormal routing of the descending motor pathways. These differences may be indicated by unusual patterns of physiological connectivity. The goal of this chapter was to investigate these patterns through time and frequency domain analyses of recordings from hand musculature.

Research into this area is important for improving our understanding of the effects of early brain damage. It may also aid in the development of a new means of assessing motor reorganisation prior to hemispherectomy. As discussed in Chapter 1, if a child does not already have a very severe hemiplegia and is being considered for hemispherectomy, clinicians may use fMRI or TMS to determine if motor reorganisation has occurred, i.e. if the cerebral hemisphere contralateral to the proposed hemisphere for resection/disconnection has assumed some control of the paretic side of the body. If motor reorganisation has not occurred, there is the potential of exacerbating the patient's disability that must be weighed against the risk of continuing, frequent seizures.

Both fMRI and TMS have their disadvantages. fMRI is costly, time-consuming and unsuitable for children who are very young or have severe behavioural problems. Furthermore, the fMRI signal is often too weak to provide conclusive evidence of reorganisation. TMS has the potential to elicit a seizure, is not available in all hospitals and may be an intimidating

procedure for a child. The approach that will be used here is inexpensive, quick, safe, requires tools that are widely available and is easily tolerated by children that are young and/or have behavioural problems.

3.1.1 Motor pathways after early brain damage

Corticospinal neurones project directly from the cortex to the spinal cord, with a majority terminating in the contralateral hemicord and only a minority (10-20%) terminating in the ipsilateral hemicord. The ipsilateral projections drive proximal musculature, whilst distal musculature is controlled predominantly by contralateral connections (Lawrence and Kuypers 1968a). Studies of both the rodent and cat have, however, demonstrated that during the early stages of development ipsilateral projections are more numerous than in the adult (Armand et al. 1996; Eyre 2007; Martin 2005; Stanfield 1992). Ipsilateral projections normally reduce in number throughout development (Alisky et al. 1992; Li and Martin 2000; Theriault and Tatton 1989), but can be preserved if the primary motor cortex of the other hemisphere is silenced during the pruning phase (Friel and Martin 2005). If the abnormal ipsilateral connections are preserved, but the unaffected cortical hemisphere is later silenced, motor performance of the ipsilateral limb is impaired (Martin et al. 2000). This indicates that the abnormal ipsilateral pathway has a functional role in motor performance. The non-silenced hemisphere assumes bilateral control of the body, to an abnormal extent.

It has been suggested that this process mirrors the effects of an early brain lesion in humans. The proposal is that humans also develop supranumeral ipsilateral corticospinal projections that are later pruned. An early brain lesion that silences the activity of one hemisphere (perhaps due to a unilateral stroke) can disrupt the pruning process, leading to the preservation of functional ipsilateral projections from the non-lesioned cortex. This hypothesis is supported by behavioural and physiological evidence. In the human neonate, the excitability of ipsilateral corticospinal neurones is abnormally high (Eyre et al. 2001), demonstrated by short-latency, ipsilateral responses to low intensity TMS. This may indicate a greater density of

ipsilateral projections. In the healthy individual, the ipsilateral responses reduce with age and plateau at three months after birth. In patients with unilateral cerebral palsy, though, fast conducting, ipsilateral responses of high amplitude can persist into adulthood (Benecke et al. 1991; Cincotta et al. 2000; Eyre 2007). If stimulation of the lesioned hemisphere does not elicit a response, then ipsilateral responses are associated with relatively better hand function (Carr et al. 1993). This suggests that in some cases, when the crossed pathway from the lesioned cortex is disrupted, abnormal ipsilateral pathways from the non-lesioned hemisphere can provide some compensation for motor control of the hand contralateral to the lesion. Furthermore, those patients with better contralateral hand function after extensive childhood brain damage to the motor cortex are likely to have incurred brain damage before or around the time of birth (Carr 1996; Carr et al. 1993). This may indicate that there is an important period of development – possibly the period before and during corticospinal pruning – where the nervous system has greater potential for adaptation. Once this period has passed, prospects for recovery may worsen.

3.1.2 Branching pathways

The ipsilateral terminations in the spinal cord could take a distinct route from the cortex than that of the crossed connections that arise from that same hemisphere. Studies of cats (Martin et al. 1999) and macaques (Rosenzweig et al. 2009) with unilateral brain injuries suggest otherwise. In these animals, ipsilateral pathways were instead found to be branches of the contralateral projections from the same hemisphere. As some of the neurones descended from the cortex to the spinal cord they had arborised, with one branch projecting to the left hemicord and the other projecting to the right. The methods used in this research are too invasive to be performed on humans. There is, though, both behavioural and non-invasive physiological evidence to suggest that a similar pattern of abnormal connectivity can occur in humans. Those patients with heightened ipsilateral corticospinal excitability, perinatal brain damage and relatively better hand function, also exhibit pathological mirror movements (Carr 1996; Carr et al. 1993). A mirror

movement is an involuntary movement on one side of the body that synchronously mimics a voluntary movement on the opposite side. Pathological mirror movements have been described in certain conditions including X-linked Kallman's syndrome (Farmer et al. 2004b; Mayston et al. 1997), Klippel-Feil syndrome (Farmer et al. 1990) and some cases of hemiparesis (Carr et al. 1993; Farmer et al. 1991). Mirror movements are also common in healthy children, but if they persist beyond the age of eleven then they are weak and unsustained (Connolly and Stratton 1968) or pathological. The mechanism of developmental mirror movements is unclear (Carson 2005), but current evidence suggests that it differs from that of pathological mirror movements.

3.1.3 Neurophysiological evidence for branching pathways

Pathological mirror movements are thought to be caused by the excitation of abnormal, branching corticospinal pathways (Farmer et al. 1991; Farmer et al. 1990). As with the studies of the cat and macaque already discussed, it is suggested that corticospinal neurones arborise on the descent from the cortex, to innervate both sides of the spinal cord and so provide a common, bilateral drive. Evidence for common drive is typically derived from EMG recordings, taken simultaneously from two muscles during a weak contraction (Sears and Stagg 1976). As will be discussed in more detail below, if two muscles are activated by a common input, then the EMG recordings may be correlated. Since there could be a delay in the time of activation, the linear correlation between the two signals can be expressed as a function of the lag of one signal relative to the other (cross-correlation). When bilateral hand muscle recordings are acquired from patients with pathological mirror movements, a peak can be observed in the cross-correlation between the two signals at or close to zero-lag, indicating that the motoneurones receive shared synaptic input, resulting in synchronous firing (Farmer et al. 1991; Farmer et al. 1990). In healthy adults, a peak can be found when recording from left and right diaphragm, rectus abdominus and masseter muscles (Carr et al. 1994). These muscles, then, are believed to have shared input from branching pathways. Unlike those patients with

pathological mirror movements, though, there is no such bilateral correlation between upper limb muscles (Carr et al. 1993; Carr et al. 1994; Farmer et al. 1990; Marsden et al. 1999). Such a correlation is also absent in the upper limbs of children with developmental mirror movements (Farmer et al. 1991; Mayston et al. 1999). The available evidence suggests then that, unlike pathological mirror movements, developmental mirror movements are not driven by a shared input from a branching pathway.

When evaluating this evidence, it is important to attend to the timing of the correlation, since it is only from consideration of the lag in the cross-correlation that one can derive claims about the point of branching. Motoneurones are brought to firing by excitatory postsynaptic potentials (EPSPs). EPSPs are caused by presynaptic input from peripheral, propriospinal or supraspinal neurones. A single presynaptic neurone may branch to synapse on many motoneurones, delivering common input (Mendell and Henneman 1968). But this is only one possible route for common input to motoneurones. Alternatively, a neurone earlier in the hierarchy, perhaps in the cortex or within the spinal cord, may branch and synapse onto multiple neurones that project to motoneurones (see Figure 8). If two motoneurones receive either form of common input then, depending on their membrane potentials, they may fire synchronously or with a short delay. If one records a sufficient number of action potentials, the correlation between the firing times of the two neurones may reach statistical significance. For this reason, if the firing time of two motoneurones is significantly correlated, one may infer that they receive common drive. This hypothesis has been tested through intracellular recordings of the EPSPs at the soma of each motoneurone (Kirkwood and Sears 1978) and the action potentials at the motor nerve filaments (Sears and Stagg 1976).

From the presence of a correlation, one cannot say with certainty at what stage in the system the signal diverged. Even if two motoneurones receive input from the same branching presynaptic neurone, there may still be a difference in the recorded time of the EPSPs or action potentials. For recordings of the EPSP, one needs to take into account the possibility of a

difference in the conduction delays between the point of branching and each soma and/or a difference in the synaptic delays. For recordings of the action potential, there may be a further difference in the conduction delays between each soma and each recording probe in the motor nerve filaments. For this reason, if shared input is present and assessed with either acquisition method, one can expect to see significant correlations over a lag range of +/- 1-3ms. If divergence happened earlier in the system the delay would not necessarily be greater, but there would be a raised probability of lag between the two signals exceeding 3ms, due to conduction and synaptic delays. For this reason previous researchers have concluded that, if the two signals are significantly correlated over a lag range of up to +/- 3ms, one can reasonably infer common drive is due to shared input from a branched, presynaptic neurone (Kirkwood and Sears 1978).

Correlations become more difficult to interpret if one records directly from the muscle tissue with needle EMG, rather than from the soma of a motoneurone or the motor nerve filaments. With such recordings there is the further possibility of a difference in the synaptic delay at the neuromuscular junction and the conduction delays between the neuromuscular junction and the recording probe. The situation is worse if recordings are made from the skin surface, as there may now also be a difference in the conduction properties of the subcutaneous tissue and skin. For these reasons, where shared input is present and recordings are made from within the tissue or on the skin, researchers may find a significant correlation with a lag of approximately +/- 12ms (Farmer et al. 1991). A significant correlation is still indicative of shared input, but with delays of this magnitude it is difficult to say with certainty where in the motor system branching has occurred.

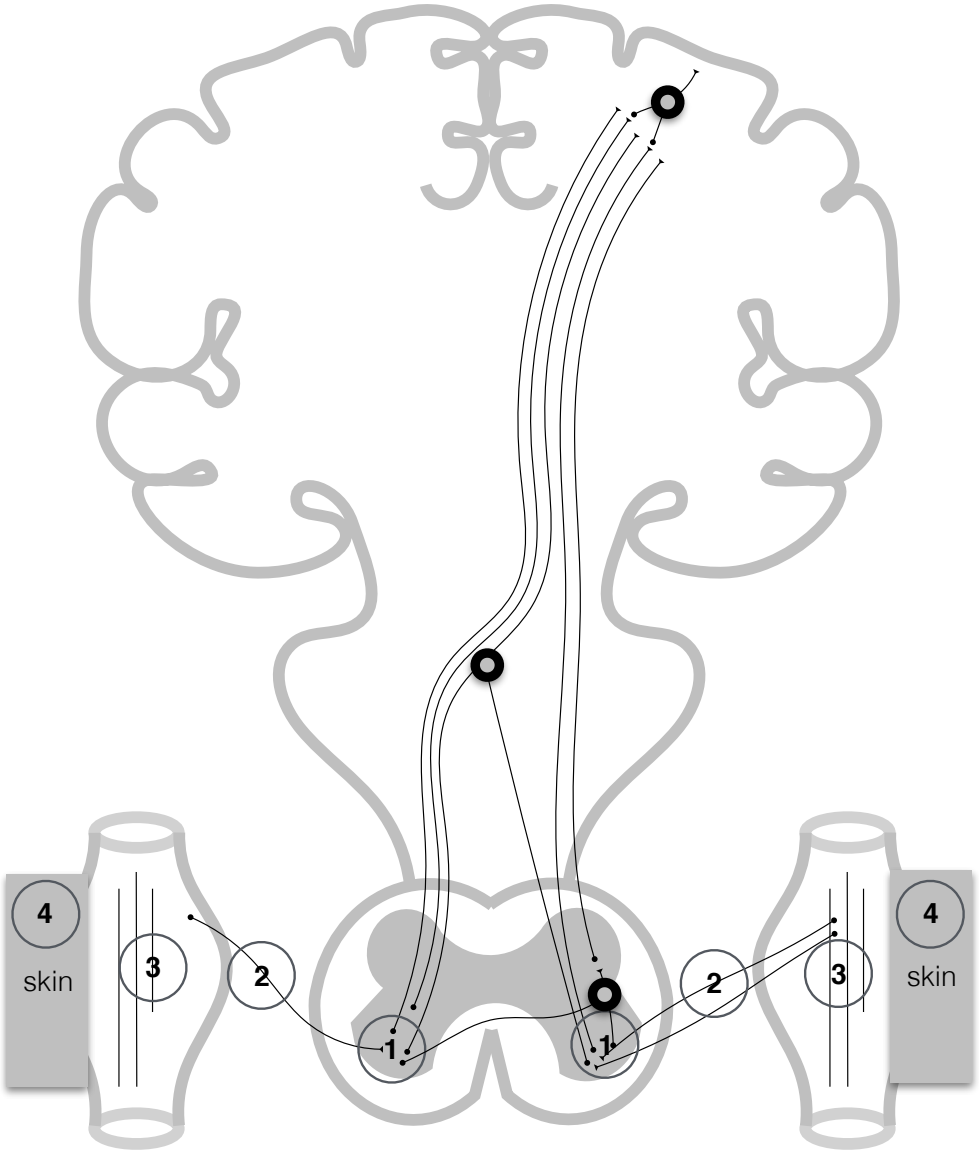

Figure 8. Schematic of neuronal branching and recording sites

Cortical control over the ipsilateral hand muscles may either be delivered along distinct uncrossed neurones or via a shared, bilateral pathway. Filled circles represent three potential points of neuronal branching: in the cortex, on the descent to the spinal cord or within the spinal cord. Previous research has attempted to determine the pattern of neuronal connectivity by comparing recordings from left and right musculature (see main text). Numbers represent potential recording sites: (1) motoneurone soma, (2) motor nerve filament, (3) within the muscle tissue, (4) on the skin.

3.1.4 Correlations in the frequency domain

Common input to the system may be aperiodic. It may also be rhythmic. It has been repeatedly demonstrated that EMG recordings of synergistic wrist and hand muscles of the same limb have common periodicities within the beta frequency band of 12 to 32 Hz (Farmer et al. 2007; Farmer et al. 1991; Keenan et al. 2012; Kilner et al. 1999). Periodic synchronisation between left and right muscles has previously been shown for patients with pathological mirror movements, namely, patients with X-Linked Kallman's syndrome (Mayston et al. 2001). To date, though, this has not been replicated in patients with hemiparesis. The frequency range of shared input may have a functional basis. Beta rhythms are also present in electroencephalographic (EEG) and magnetoencephalography (MEG) recordings of the motor cortex during maintained isometric contraction (Penfield 1954). Simultaneous surface recordings from hand musculature correlate with brain recordings within this frequency band, suggesting a periodic interaction between brain and muscle (Conway et al. 1995; Halliday et al. 1998). It has been proposed, then, that beta rhythms in hand musculature reflect the influence of cortical drive. Whilst correlations in the time domain can be estimated with cross-correlation, correlations in the frequency domain can be estimated with coherence analysis.

Coherence is a normative measure of linear association between the frequency components of two signals, measured on a scale from 0 to 1. Coherence between two signals can be estimated by, firstly, dividing each signal into non-overlapping segments. Secondly, for each segment of each signal, applying a fast Fourier transform to estimate the amplitude of the frequency components of the segment. Thirdly, an estimation of the power of each signal at each frequency (the auto spectra) can be computed by averaging the amplitude of each frequency component across all segments of each signal. Fourthly, an estimation of the average power of the two signals at each frequency (the cross spectrum) can be computed. Lastly, the coherence of the two signals can be estimated from the magnitude squared of the cross spectrum normalised by the product of the auto spectra. It is

possible to estimate a measure of correlation in the time domain that is analogous to cross-correlation – the cumulant density – by taking the inverse Fourier transform of the cross spectrum. This method allows one to estimate confidence limits (Halliday et al. 1995).

3.1.5 Mirror movements and hemispherectomy

To summarise, this review has provided evidence that early childhood brain injury can result in the preservation of abnormal ipsilateral corticospinal pathways. It was shown that, when the lesioned motor cortex appears to be non-functional, the presence of such pathways is associated with better hand function, but also pathological mirror movements. Physiological evidence has been presented that suggests that these pathological mirror movements are caused by common drive along descending motor pathways. This can be assessed using coherence and cross-correlation/cumulant density estimates. It may be the case, then, that after childhood brain injury, better hand function can be partially preserved by the abnormal development of bilateral drive from the non-lesioned cortex.

These findings may help to explain why some patients retain hand function after hemispherectomy. As with other patients with childhood onset hemiparesis, where investigated, hemispherectomised patients with hand function post-surgery have presented with mirror movements that persist into adulthood (Holloway et al. 2000; Honda et al. 2010; Müller et al. 1991; Pascoal et al. 2013; Pilato et al. 2009; Rutten et al. 2002; Zsoter et al. 2012). Few studies have assessed mirror movements pre-hemispherectomy but, when mirror movements have been reported, hand function has been either unchanged or improved by surgery (Pilato et al. 2009; Rutten et al. 2002; Zsoter et al. 2012). It is proposed, then, that hand function contralateral to the resected hemisphere is preserved after hemispherectomy if the descending motor pathways have adapted to an early lesion by retaining bilateral projections from the non-lesioned cortex. In the current study, this was assessed using the methods that were detailed above. Firstly, patients were assessed for the presence of mirror movements using a behavioural protocol.

Secondly, the presence of branching pathways was assessed by analysing muscle recordings acquired from the skin overlaying the wrist extensors of patients. It was expected that muscle activity in the left and right wrists would be correlated in both the time and frequency domains. Since this approach uses recordings made from the skin surface it was not possible to identify the branching point; nonetheless a correlation between the recordings would demonstrate a common input.

3.2 Methodology

3.2.1 Participants

The tests were attempted by all six hemispherectomised patients, however due to impaired motor function some patients were unable to complete some of the tasks (details are provided in the results section). As described in Chapter 2, motor assessments of the weaker arm found E.B. and H.W. were the least impaired, P.O. and D.N. were ranked in the middle and J.S. and C.B. were the most impaired. According to their clinical histories (see Chapter 2), mirror movements were first detected in E.B. during her pre-operative assessment and, when asked, reported them as “always being present”. No pre-operative assessments were available for H.W., though mirror movements were assessed and detected post-operatively. Previous research has found mirror movements to be absent for C.B., and a published study reported them as absent for P.O. (Vargha-Khadem et al. 1997). The clinical histories of D.N. and J.S. have no reference to the assessment of mirror movements. A comparison group also took part in the EMG recordings, consisting of twelve age and sex matched individuals (age range, 19–37 years; mean age, 27 years; six male; one left-handed) with no history of neurological or psychiatric disorder and with normal or corrected-to-normal vision. Healthy participants were contacted through an online advertisement at University College London. All healthy and patient participants were paid £20 for taking part in the study.

3.2.2 Behavioural testing

Patients were tested for the presence of mirror movements with the method devised by Woods and Teuber (1978). Each participant was asked to perform three different joint rotations with each hand in turn: (1) rapid tapping of the index finger on the distal joint of the thumb on the same hand; (2) rotation of the fist by alternating pronation-supination of the forearm; (3) repetitive alternate touching of each fingertip to the tip of the thumb of the same hand. During testing, the participant sat with elbows resting on a table and forearms straight up. Mirror movements elicited in the contralateral hand

were scored on an ordinal scale as: 0 = no clear imitative movement; 1 = barely discernible imitative movement; 2 = obvious but unsustained movement; 3 = strong and sustained imitative movement; 4 = movement equal to that observed in the intentionally active hand.

3.2.3 EMG recordings

EMGs were recorded from left and right extensor carpi radialis during wrist extension whilst the participant attempted to hold a steady, bilateral wrist extension at approximately 10% of maximum voluntary contraction. EMGs were acquired with pre-gelled, disposable, Ag-AgCl, EL501 snap electrodes with the Biopac MP35 data acquisition unit and the Biopac Student Lab PRO 3.7 software (Biopac Systems, Goleta, CA, USA). To ensure correct electrode placement, the experimenter palpated each muscle whilst the participant contracted and relaxed. To ensure optimal contact during recording, non-conductive skin cells were removed from the skin area overlying each muscle by scrubbing with an ELPAD abrasive pad (Biopac Systems, CA, USA). Two electrodes were attached along the length of each muscle belly separated by a distance of 2 cm and a reference electrode was attached to each olecranon. The electrodes were then connected to the amplifier with Biopac SS2L leads (Biopac Systems, CA, USA). EMGs were recorded at a sample rate of 2 kHz with a hardware bandpass filter (5 to 500 Hz).

3.2.4 Data analysis

Time and frequency domain analyses of the data were performed in Matlab 2015a using the methods detailed in Halliday et al. (1995). Since muscle contractions were not sustained throughout the recordings, sections of contraction of at least 512ms duration were identified with a custom Matlab script and passed through for analysis. Signals were full wave rectified. It has been shown that rectification maximises the information regarding timing of motor unit action potentials whilst suppressing information regarding waveform shape (Ward et al. 2013). Mains suppression was applied to remove signal noise at ~50 Hz and the data were de-trended. Auto spectra

and cross spectra were estimated by averaging the discrete fast Fourier transforms from non-overlapping segments of data taken from each recording. Correlation between the signals in the frequency domain (1-100Hz) was calculated as a function of the coherence, estimated from the magnitude squared of the cross spectrum normalised by the product of the auto spectra. Correlation in the time domain over a range of time lags (±100 ms) was calculated as a function of the cumulant density, defined as the inverse Fourier transform of the cross spectrum. In order to evaluate the significance of coherence and cumulant density estimates, upper 95% confidence limits were calculated for coherence plots and upper and lower 95% confidence limits for cumulant density plots, as per Halliday et al. (1995). For ease of comparison the cumulant density values were normalised to the upper and lower confidence limits, so that for all participants the upper and lower confidence limits were equal to +1 and -1, respectively.

3.3 Results

3.3.1 Mirror movements

C.B. and J.S. could not perform any of the mirror movement tasks with the weaker hand. When performing the tasks with the stronger hand, no mirror movements were evoked in the weaker hand. P.O. could not perform any of the tasks with the weaker hand. Both forms of finger tapping with his stronger hand elicited weak (grade 1) mirror movements in his weaker hand, though none were evoked by wrist rotation. D.N. could tap the index finger and thumb of his weaker hand, albeit with great difficulty. This elicited weak (grade 1) mirror movements in his stronger hand. He could not perform any of the other tasks with his weaker hand. Finger-thumb tapping with his stronger hand also elicited weak (grade 1) mirror movements in his weaker hand, but no mirror movements were evoked by the other tasks. H.W. could perform all the tasks with her weaker hand, but only fist rotation elicited mirror movements (grade 3). All tasks with the stronger hand elicited mirror movements in the weaker hand (grades 3 or 4). E.B. could also perform all tasks with the weaker hand. All tasks evoked strong (grade 4) mirror movements in the contralateral hand. The same was true when performing the tasks with her stronger hand.

3.3.2 Time and frequency domain analyses of EMGs

Due to the profound weakness in their hand musculature, all patients found it difficult to maintain sustained contractions for the recording of EMGs. Only the recordings acquired from E.B., H.W. and P.O. provided sufficient data for analysis. Figure 2 to Figure 5 provide selections of the rectified EMG acquired from each of these patients and one example healthy participant, along with the auto spectra, cumulant density, coherence and phase.

The cumulant density functions estimated for the healthy participants did not reveal significant peaks (see Figure 9). Similarly, the cumulant density plot for P.O. (see Figure 10) did not indicate a significant association between the left and right muscle recordings. In contrast, analysis of E.B.’s recordings (see Figure 12) revealed a symmetrical, central peak in the cumulant density

function that extends from -10.5ms to 10.5ms lag. Similarly, for H.W., there is a central peak in the cumulant density of ±10ms (see Figure 11).

The coherence functions estimated for the healthy participants did not have significant peaks, either (see Figure 9). Again, similar to the healthy participants, the coherence between the left and right EMG recordings of P.O. was not statistically significant for any frequency (see Figure 10). In contrast, in the coherence plot of E.B., left-right EMG coherence is identified in frequency ranges 1-4 Hz, 8-12 Hz and 28-31 Hz i.e. at low frequency, alpha and high beta frequency ranges (see Figure 12). The phase plot shows the signals to have approximately zero phase-offset over these frequencies. H.W. (see Figure 11) showed strong left-right EMG-EMG coherence with maxima at 10 Hz, 18 Hz, 22 Hz and 42 Hz and associated zero phase lag over the frequency range 4-56 Hz.

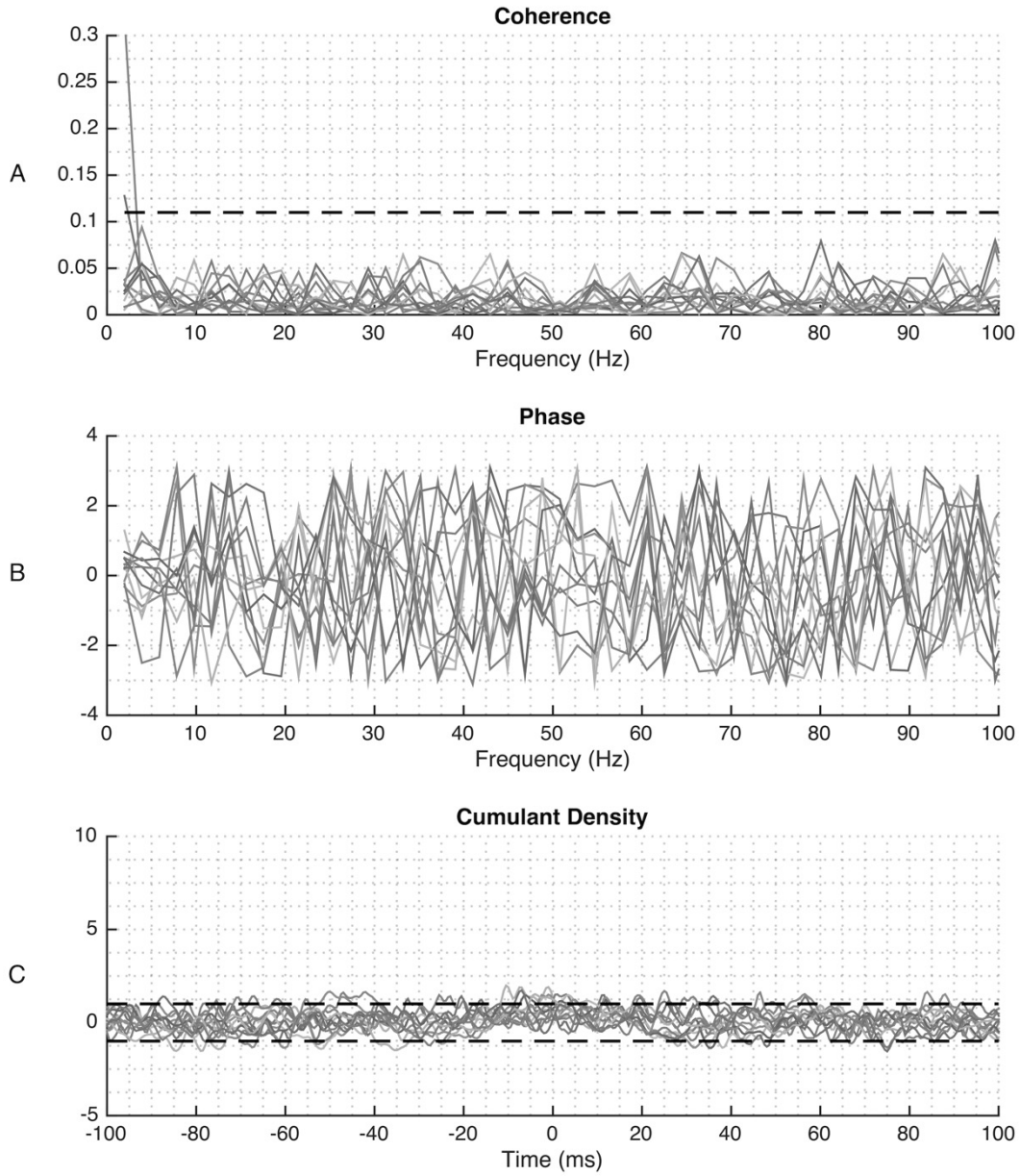

Figure 9. Analysis of EMG data: comparison group

Time and frequency domain analysis for all twelve members of the comparison group, including: (a) coherence, (b) phase lag (radians) and (c) cumulant density, between rectified surface electromyograms recorded from the left and right extensor carpi radialis. The horizontal dashed line in the coherence estimate is the upper 95% confidence limit based on the assumption of independence. In the cumulant density plot, the dashed horizontal lines indicate the upper and lower 95% confidence limits.

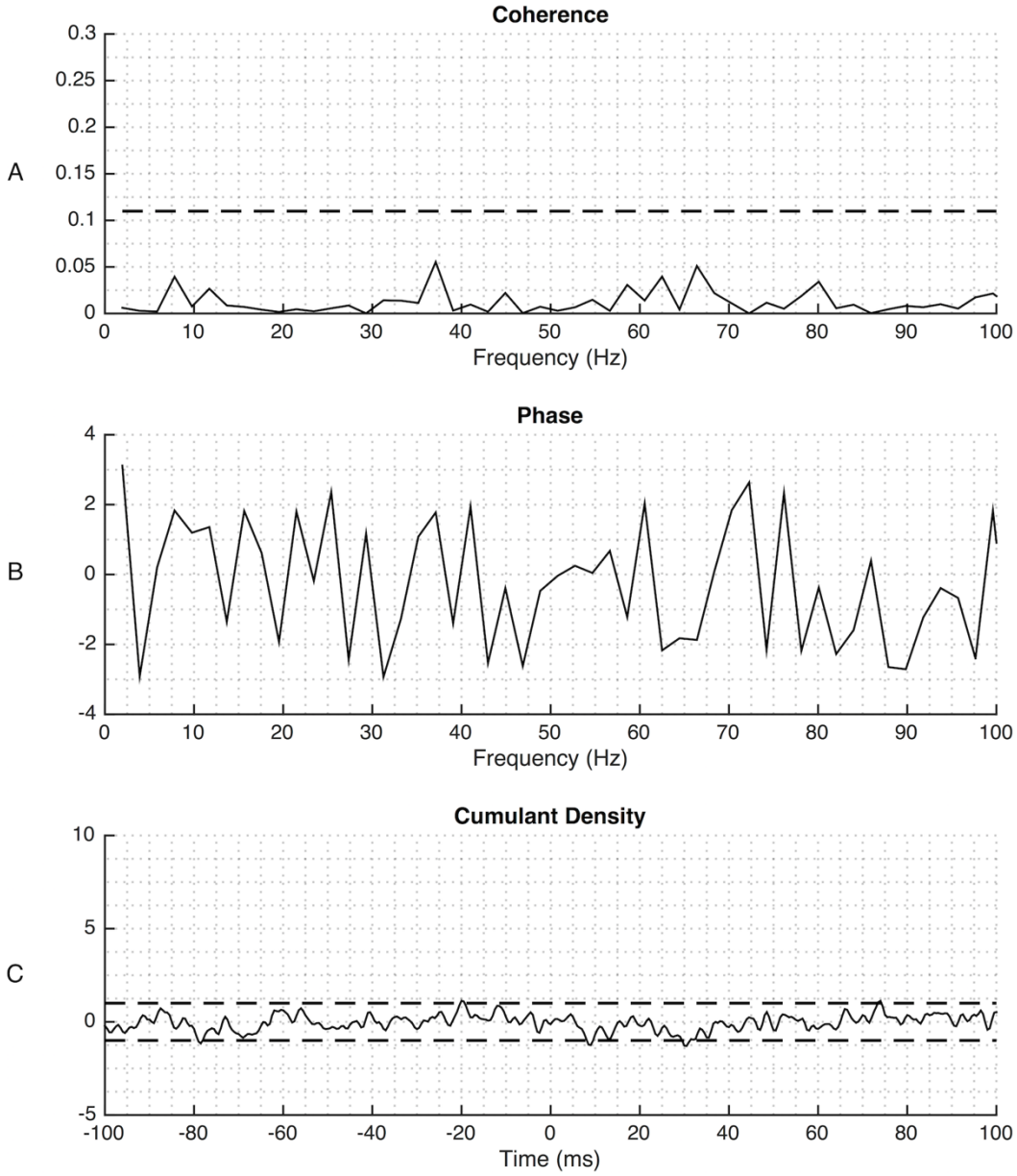

Figure 10. Analysis of EMG data: P.O.

Time and frequency domain analysis for P.O., including: (a) coherence, (b) phase lag (radians) and (c) cumulant density, between rectified surface electromyograms recorded from the left and right extensor carpi radialis. The horizontal dashed line in the coherence estimate is the upper 95% confidence limit based on the assumption of independence. In the cumulant density plot, the dashed horizontal lines indicate the upper and lower 95% confidence limits.

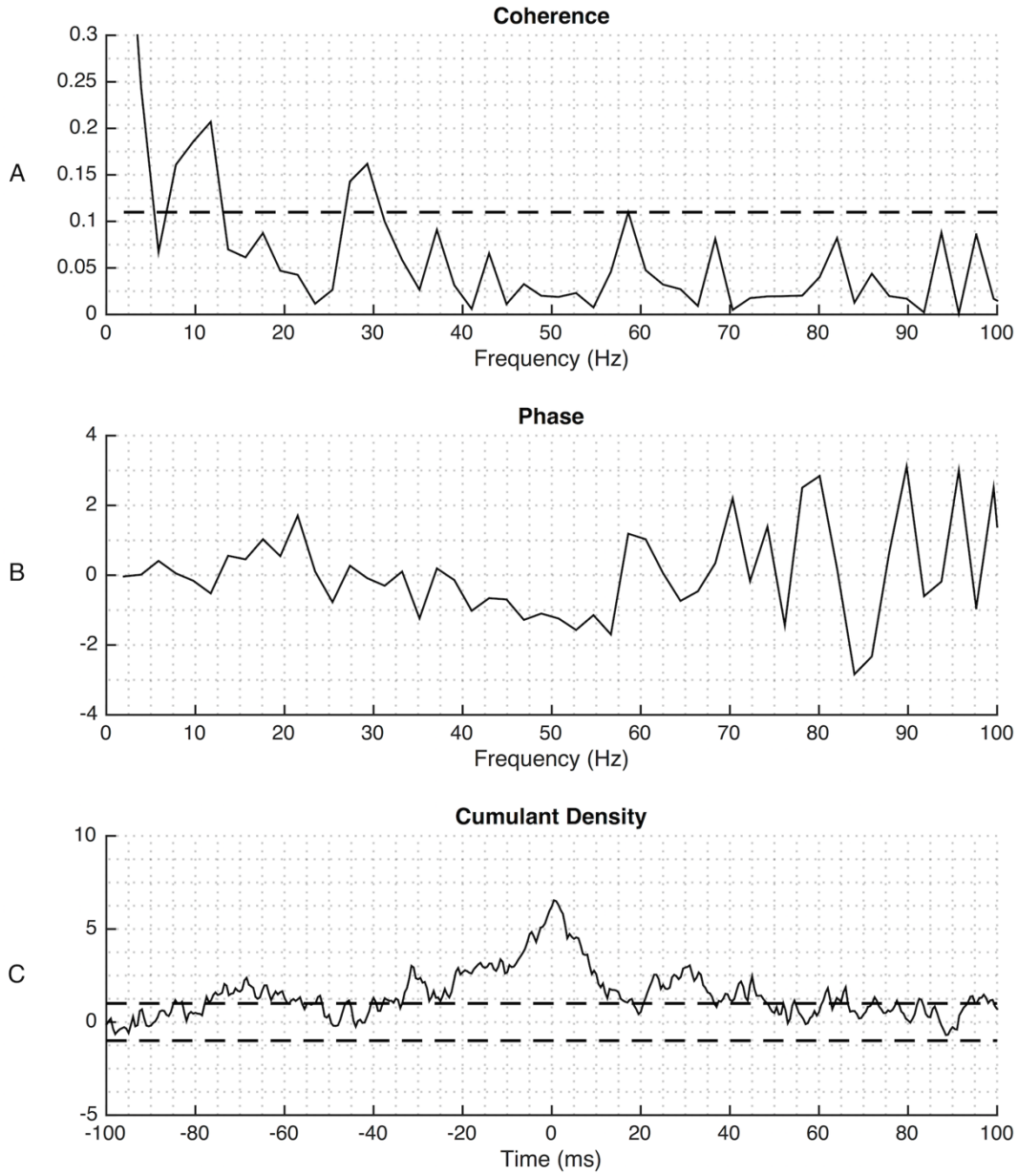

Figure 11. Analysis of EMG data: H.W.

Time and frequency domain analysis for H.W., including: (a) coherence, (b) phase lag (radians) and (c) cumulant density, between rectified surface electromyograms recorded from the left and right extensor carpi radialis. The horizontal dashed line in the coherence estimate is the upper 95% confidence limit based on the assumption of independence. In the cumulant density plot, the dashed horizontal lines indicate the upper and lower 95% confidence limits.

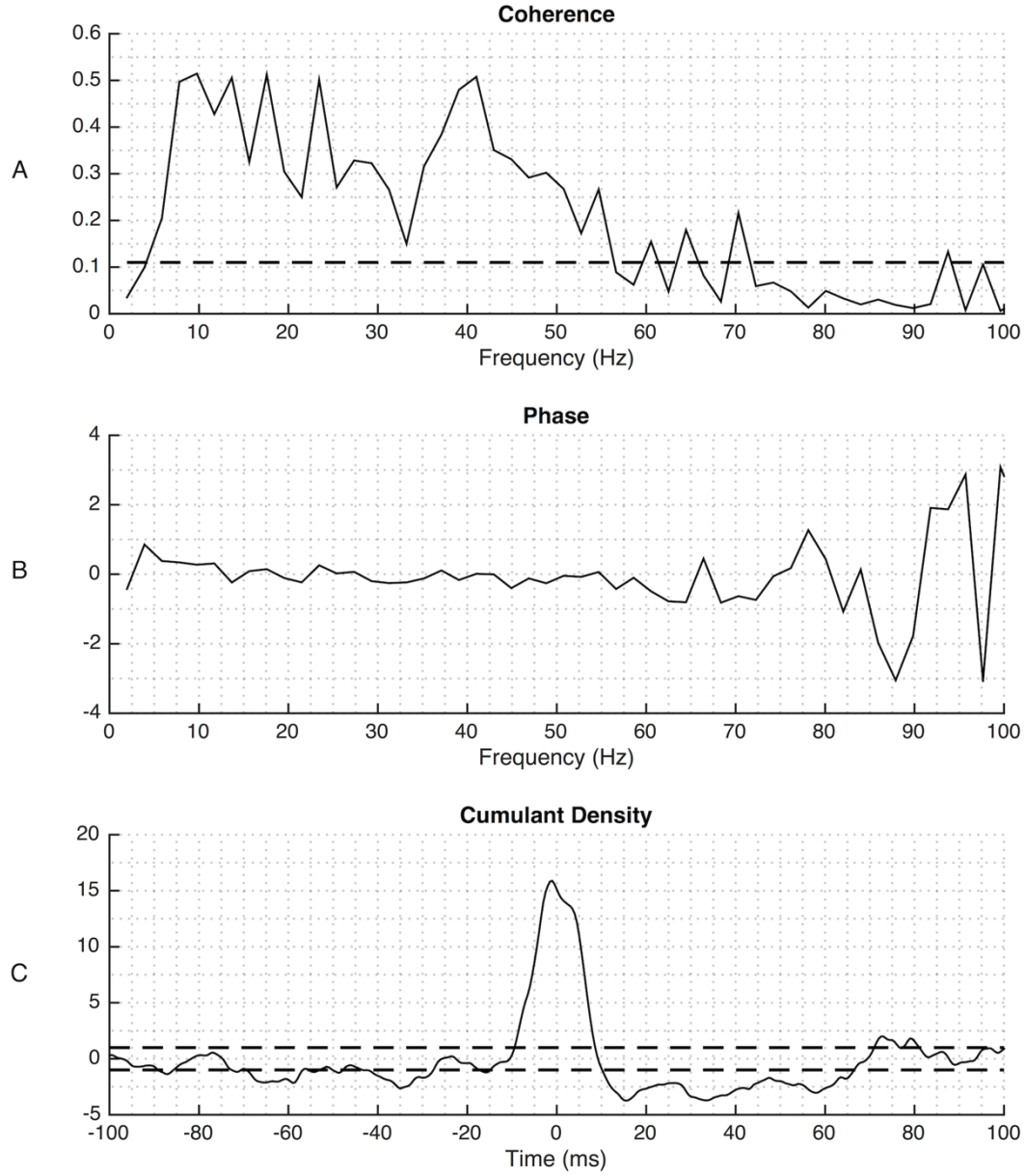

Figure 12. Analysis of EMG data: E.B.

Time and frequency domain analysis for E.B., including: (a) coherence, (b) phase lag (radians) and (c) cumulant density, between rectified surface electromyograms recorded from the left and right extensor carpi radialis. The horizontal dashed line in the coherence estimate is the upper 95% confidence limit based on the assumption of independence. In the cumulant density plot, the dashed horizontal lines indicate the upper and lower 95% confidence limits.

3.4 Discussion

In the previous chapter it was observed that E.B. and H.W. have maintained relatively good hand function after hemispherectomy. It was hypothesised that this is due to the preservation of branching ipsilateral pathways that project from the remaining hemisphere of the cortex to the spinal cord, that could themselves result in mirror movements. In this chapter we have seen that H.W. and, in particular, E.B. exhibit moderate or strong mirror movements and both have a history of them – for E.B. they were noted prior to surgery. Analysis of EMGs obtained from the patients showed the left and right wrist muscles to have a common input. During bilateral contraction, motor units on left and right sides fired approximately synchronously, with maximum lags between the correlated components of the signals of approximately +/- 10ms. These values are similar to those observed in previous studies of mirror movements and branching pathways (Farmer et al. 1991). As described in the introduction to this chapter, the delay can be attributed to factors such as conduction and synaptic delays. The left and right signals were also found to have common oscillations, at both alpha and beta rhythms. Periodic synchronisation between left and right muscles has previously been shown for patients with X-Linked Kallman's syndrome (Mayston et al. 2001), but this is the first time that bilateral EMG coherence has been shown for hemiparetic patients. The frequency range of shared input may have a functional basis. As reviewed in the introduction, alpha rhythms may correspond with the frequency range of neurogenic tremor (Elble and Randall 1976), whilst beta rhythms are believed to reflect cortical drive to muscles (Conway et al. 1995; Halliday et al. 1998). Together, these results indicate that both E.B. and H.W. have shared input to left and right muscles of the distal upper limb that may be due to branching, descending motor pathways, although due to the lag duration it is not possible to identify the point of branching.

The hand and wrist function of the remaining patients was worse, with combined scores for wrist and hand tasks on the Fugl-Meyer Assessment ranging from 4 to 7 out of 24. C.B. and J.S. did not exhibit any mirror

movements, but were unable to perform any of the behavioural tasks here with the weaker hand. Weak mirror movements were detected in D.N. and P.O. In D.N.'s clinical history, there are no reports of mirror movements being tested previously and very little testing of motor function. In a previous case-study of P.O., no mirror movements were detected (Vargha-Khadem et al. 1997). This may be because they were particularly weak and only present as involuntary movements in the stronger hand during voluntary use of the weaker hand. In this study, weaker mirroring accompanied actions that were performed with moderate or extreme difficulty. No association was found between left and right motor units during these actions, however, in the time or frequency domains. It should be noted that the absence of a significant association between two muscle recordings is not conclusive evidence for absence of shared input. Previous research has shown that occasionally an association between the excitatory postsynaptic potentials of two motoneurones may be found when an association between simultaneous EMG recordings of those motor units is absent (Kirkwood and Sears 1978). Whilst the EMG data appear to indicate that the left and right wrist extensors of P.O. do not receive shared, bilateral input, this negative finding should be approached with at least some caution.

Still, since some of the patients were able to perform some of the tasks with the weaker hand without mirroring and analysis of the EMG data from one of the patients (P.O.) found no evidence of a common drive to left and right wrist extensors, this suggests that two patterns of adaptation may exist. The first, a system of branched neurones providing shared input to left and right motoneurones was identified within those patients with superior hand function. The second route – non-branching ipsilateral projections from the intact cortex to hand musculature – may also exist, but may be insufficient for the type of ability exhibited by E.B. and H.W. after hemispherectomy.

This theory is supported by a study of patients with unilateral cerebral palsy. Carr and colleagues (1993) demonstrated that patients with a bilateral muscle response to stimulation of the intact motor cortex could be divided into two categories on the same basis: those with superior hand ability,

intense mirror movements and evidence of shared input to left and right musculature; and those with lower ability, no intense mirror movements and no evidence of shared bilateral drive. Here it has been shown that this categorisation is applicable to hemispherectomised patients, where the operated hemisphere can perform no possible function.

This distinction could be used as a measure of motor reorganisation when evaluating the risk that hemispherectomy poses to hand function. It would be particularly beneficial, then, to ask if the presence of mirror movements pre-surgery is a necessary and sufficient condition for contralesional hand function post-surgery. For this, pre-surgical assessment of mirror movements is needed. To test this systematically a longitudinal study would be required. It is hoped that others will pursue this line of enquiry.

In summary, it has been shown that strong mirror movements can be related to superior hand ability after hemispherectomy. The predominant mechanism was found to be a common drive to left and right hand musculature. The electrophysiological methods that were employed here can provide clinicians with a technique for testing the presence of shared input. The protocol is easy to administer, the tools are widely available and the results may enable clinicians to deliver a more accurate prognosis when considering a candidate for hemispherectomy.

4. Kinematic assessment of bimanual and unimanual reaching

AIM. To assess functional unimanual and bimanual reaching after hemispherectomy in terms of upper limb kinematics.

METHOD. Bilateral forearm movement was recorded from six hemispherectomised patients (age 20-36 years; three male; five left-handed) whilst they performed unimanual and bimanual tasks, with and without visual feedback. Movement time, average speed, maximum speed, length index, number of movement units, bilateral onset lag and bilateral end lag were calculated. Effects of condition were compared to twelve typically developed age and sex matched controls (age 19-37 years; six male; one left-handed) using mixed effects regression modelling.

RESULTS. Relative to the comparison group, average and maximum speed of the patient group's paretic arm were lower than the non-paretic arm, whilst number of movement units and length index were higher. Reaching with the non-paretic was not significantly different to the comparison group's dominant arm. The patient group's arms were less synchronised at action onset and end. In fact, patients performed many bimanual trials sequentially. Random effects estimates showed some patients performed significantly differently to group averages.

INTERPRETATION. Motor control of the paretic, but not the non-paretic, arm is severely impaired after hemispherectomy, but individual impairments can differ significantly from group averages. Bimanual synchronisation is disrupted, possibly due to the demands of controlling both arms with one hemisphere, but spatial interference appears to be preserved suggesting reorganisation to an intra-hemispheric network for control of both arms.

4.1 Introduction

In Chapter 2, a group of patients was introduced who had undergone hemispherectomy as treatment for intractable epilepsy. The clinical history of each patient was discussed, with an emphasis on their motor impairments. Chapter 2 provided an up to date assessment of these impairments using standard clinical outcome measures. It was shown that, whilst these patients were most impaired at complex tasks involving the upper limb contralateral to the resected/disconnected hemisphere, they could perform gross movements with this arm. For some patients, the hand could still be used functionally and Chapter 3 suggested that this was due to the presence of branching motor pathways from the unoperated hemisphere. For one patient, C.B., the outcome measures of Chapter 2 also detected impairments in the upper limb ipsilateral to the resected hemisphere, but this was only in terms of fine motor control. Furthermore, all patients were found to have significant visual deficits, not only affecting the hemifield contralateral to the side of surgery, but also partially affecting the ipsilateral hemifield.

In this chapter, the patients' motor impairments will be investigated further with movement analysis. Three themes will be examined. Firstly, unimanual motor performance will be investigated for a simple, self-paced reaching task. The capacity of the patients to execute a bimanual action will be explored. Since neural control of both arms must come from one side of the cortex after hemispherectomy, patients may find it difficult to simultaneously implement and direct movements of both arms. The lag between the arms at movement onset and end will be calculated, along with differences in the spatial trajectory of the arms during bimanual movement, compared to a unimanual action. Other factors that may influence the kinematic variables will also be accounted for, including target distance, practice effects, fatigue and the contribution of vision. Since the patients have severe visual deficits this may further impede their capacity to carry out an action. For this reason, the contribution of vision will be assessed by asking patients to perform the task blindfolded. §

As discussed in Chapter 1, there have been many accounts of the motor impairments of the limb contralateral to the hemispherectomised patient's operated hemisphere. These deficits have often been characterised and quantified with clinical outcome measures, but these tools have limitations. They use ordinal scales that are problematic for statistical analysis, they can be susceptible to floor, ceiling and clustering effects and, perhaps more importantly, there is no outcome measure that has been designed specifically for this cohort. Motion capture provides a means of measuring the performance of patients on a high fidelity, continuous scale that could be used to complement the results of standard outcome measures. So far, only one report exists that has investigated the motor performance of a hemispherectomised patient with motion capture (Müller et al. 1991). A brief investigation of reaching movements found abnormal synergic coupling between the shoulder and elbow joint of the arm contralateral to the operated hemisphere, with greater movement from the shoulder and decreased rotation from the elbow. In order to provide further insight into the upper limb kinematics of hemispherectomised patients and to demonstrate the benefits of integrating movement analysis into standard clinical assessment, this study will provide the first movement analysis of a group of hemispherectomised patients. Performance at a reaching task will be measured in terms of movement time, speed, length index of the arm's trajectory and the number of movement units taken to complete the reach.

Whilst deficits in the arm contralateral to the operation are well known, what may be unexpected is that motor impairments can also be found in the ipsilateral arm. This arm is often referred to as 'the unaffected/unimpaired arm' (Choi et al. 2010; Rutten et al. 2002; Steenbergen et al. 2000b), but these terms are misleading. Colebatch and Gandevia (1989) showed that in adult stroke patients with hemiparesis, force from the arm ipsilateral to the lesion was impaired, most profoundly for the proximal muscles. This may be related to the connectivity of descending motor pathways. Whilst distal muscles receive drive from the crossed components of the corticospinal tract, proximal muscles also receive bilateral corticospinal and indirect descending

connections (Lawrence and Kuypers 1968a). Hence, whilst unilateral damage has the most profound effect on contralateral muscles that are distal, the effect on the ipsilateral side may be greater for proximal musculature. Tests of dexterity have detected deficits of the ipsilateral arm in patients with hemiplegic cerebral palsy and adult stroke, including tapping (Prigatano and Wong 1997) and sorting pegs (Desrosiers et al. 1996). Performance has been investigated for hemispherectomised patients too. Dijkerman et al. (2008) found the ipsilateral arm to be impaired in terms of strength and tapping speed. Findings have not been consistent between studies (Haaland and Harrington 1994), though, and deficits may only be present in some patients: from a sample of 20 hemiplegic children, only 30% showed impairment of the ipsilateral upper limb when carrying out a peg-sorting task (Dellatolas et al. 2005).

Deficits of the ipsilateral arm have also been found in terms of upper limb kinematics. For both hemiparetic adult stroke and cerebral palsy patients, movements tend to be longer in duration, with lower mean and peak speed (Hermsdorfer et al. 1999a; Hermsdorfer et al. 1999b; Schaefer et al. 2007) and disrupted in terms of the smoothness of the trajectory (de Paiva Silva et al. 2014; Nakamura et al. 2008; Yarosh et al. 2004). To date, though, no studies have investigated the kinematics of the non-paretic arm after hemispherectomy. Given the profound deficits in their paretic arm, hemispherectomised patients are highly dependent on their non-paretic arm. Impairments in this arm might, then, further impact their ability to perform functional tasks. If the arm is presumed to be unaffected, rehabilitation might neglect the non-paretic arm, or even adopt strategies that could exacerbate their impairments (Basu and Eyre 2012). For this reason, it is important to know if the movement properties of the non-paretic arm are abnormal in hemispherectomised patients. This study provides the first investigation.

4.1.1 Inter-limb synchronisation

Research into motor impairment often concentrates on the performance of unimanual tasks, but many everyday tasks depend critically on bimanual

coordination. Bimanual arm coordination can be thought of in the spatial domain as the organisation of the left and right limb trajectories and, in the temporal domain, as inter-limb synchronisation. In fact, the tendency toward inter-limb synchronisation during bimanual movement leads to the undermining of a principle of motor control. According to Fitts' law, the duration of a movement depends on the ratio of movement amplitude to target width (Fitts 1954). From this one would predict that, if the left arm were to perform a movement that is similar in amplitude but greater in the required precision than the right arm, movement duration would be greater for the left arm. But Kelso and colleagues showed that this principle is violated when the two arms perform a symmetrical bimanual movement that differs in terms of difficulty for the two arms – the movement onsets and ends tend toward synchrony, hence the movement durations tend toward parity (Kelso et al. 1979). The arm performing the easier movement extends its movement duration to match the arm performing the harder movement. Kelso et al. concluded that the central nervous system coordinates the two arms as if they were a single unit.

Subsequent studies showed that Kelso's hypothesis is itself violated when the action is asymmetrical, since movement durations were shown to differ between the arms (Fowler et al. 1991; Marteniuk et al. 1984). Under these circumstances, though, movement of the two arms may not be considered entirely independent. Compared to unimanual action, both the movement duration and end position of the arms can still exhibit a degree of bilateral influence, tending toward that of the other arm, with the effect being greater on the arm performing the easier task (Marteniuk et al. 1984). Furthermore, Fowler et al. (1991) found that, whilst movement duration differs between the arms, movement onset and peak initial acceleration tend to be synchronised. This is true for both relatively artificial (Kelso et al. 1979; Marteniuk et al. 1984) and commonplace visually guided tasks (Kazennikov et al. 2002).

The mechanism behind inter-limb synchronisation is still debated. Ivry and Hazeltine (1999) proposed that it is achieved through the integration of distinct signals for the left and right limbs. Two separate timing cues are

generated, but these signals do not have direct access to the motor system. Instead, they are routed through a shared output gate. When the output gate is triggered, cues are sent to the motor system synchronously for the left and right limbs, resulting in inter-limb coupling in the temporal domain. Ivry and Hazeltine suggested that the signals are routed to the cerebellum, which performs the gating function, rather than being sub-served by a pathway between the cerebral hemispheres. Patients who have undergone resection of the corpus callosum continue to exhibit strong coupling during bimanual movement (Franz et al. 1996a; Tuller and Kelso 1989), whilst patients with cerebellar lesions have decreased inter-limb synchronisation (Franz et al. 1996b; Ivry and Keele 1989).

This proposal suggests that, in healthy subjects, synchronisation at movement onset can be generated internally. It might be presumed, then, to be independent of factors such as vision, and preserved when blindfolded. If an action is ballistic, being entirely pre-planned without vision, synchronisation may also be present at movement end when blindfolded. If, on the other hand, the action utilises visual feedback for corrective sub-movements to achieve movement end synchronisation, then the arms may tend away from movement end synchrony when blindfolded (Fowler et al. 1991). Studies of monkeys and healthy humans have found synchronisation at movement end, for a multi-joint, everyday action, to not be just preserved without vision, but enhanced (Kazennikov et al. 2002; Kazennikov et al. 1994; Perrig et al. 1999).

These investigations of the inter-limb synchronisation of healthy participants are interesting to compare to those of patients with hemiparesis. When patients with hemiparesis, who can perform a reaching task with their paretic arm, attempt a unimanual action, the movement duration of the paretic arm is expected to be greater than the non-paretic arm. For a symmetrical bimanual action, then, based on the previous considerations one might expect that the non-paretic arm would slow down and match the reach duration of the paretic arm in order to achieve inter-limb synchronisation. Previous studies have found this to be the case (Steenbergen et al. 1996; Sugden and Utley 1995).

As with healthy participants, they have also found synchronisation to be reduced for an asymmetric bimanual task. There is an important difference though: the breakdown in synchronisation for an asymmetric task is greater for hemiparetic patients. The period over which movement of the two arms coincides is statistically significantly less than controls, whilst the latency between the two hands completing their assigned components of the task is higher (Hung et al. 2004; 2010). If inter-limb synchronisation is disrupted, then it may improve with training. Hung et al. (2011) found that, for patients with unilateral cerebral palsy, the period of bimanual overlap increases with practice, whilst the end-time latency decreases.

4.1.2 Spatial interference

Whilst one form of bimanual integration may lead to temporal synchronisation, another form may result in spatial mirroring. If an action is intended to be symmetric, this may be no bad thing, but for asymmetric action the movement of one arm may disturb the intended movement of the other. For example, motor performance during continuous circle drawing is better when the two hands move symmetrically rather than asymmetrically (Semjen et al. 1995); drawing a circle with one hand whilst simultaneously drawing a square with the other is also difficult (Franz et al. 1996a); and trying to simultaneously rub your stomach and pat your head is tricky and confusing. These are all signs of spatial interference.

Callosotomised patients have a remarkable ability to perform distinct left and right arm movements without the signs of spatial interference (Carson et al. 1997; Franz et al. 1996a; Semjen et al. 1995). For this reason, it has been proposed that the mechanism behind spatial interference is the interhemispheric transfer of spatial motor commands for the left and right limbs via the corpus callosum (Franz et al. 1996a). In healthy subjects, spatial interference is well established for rather artificial actions, designed for experimental testing in the laboratory (Carson et al. 1997; Semjen et al. 1995). The effect might also be present for everyday, functional bimanual tasks when the actions of the arms are asymmetric, represented by a change

in the limb's trajectory. This will be investigated here, providing an important functional perspective on a phenomenon that is normally only investigated for non-functional tasks.

Of course, unlike healthy participants hemispherectomised patients only use one hemisphere of the cortex. The corpus callosum is severed and redundant. It is unclear, then, if spatial interference would persist in hemispherectomised patients. If so, it would suggest that processes for motor control of the two arms – reorganised to be located within the same cerebral hemisphere – communicate through an intra-cortical pathway. This intra-cortical pathway might be equivalent to the inter-cortical pathway of healthy participants. To address this question, it was asked if the trajectory of a limb differs between a unimanual and an equivalent bimanual task and whether this effect varies between the comparison and patient group.

4.1.3 Vision

In Chapter 2 it was demonstrated that the patients that participated in this study have profound visual impairments, not only affecting the hemifield contralateral to the operated hemisphere, but the ipsilateral hemifield too. Motor control can be highly dependent on visual awareness of one's environment and body, though the extent can vary according to the task. Some tasks may require a great deal of visual information for both planning an action and online feedback during execution. For these reasons, one may expect the kinematics of a hemispherectomised patient's upper limb movement to be disrupted not only by their motor impairments, but the loss of visual information too. This may mean that under normal circumstances, when planning and executing an action they are less able to utilise the information from the visual scene. In other words, their motor performance may have a lower dependence on vision and so removal of vision would have less of an effect than on a healthy participant.

The dependence of motor performance on vision can be estimated by comparing performance under normal conditions to performance when blindfolded. Previous studies have found that healthy participants have lower

mean and peak speed for blindfolded reaching (Berthier et al. 1996; Carella et al. 2003; Perrig et al. 1999). Furthermore, Berthier et al. (1996) found that lower speed when blindfolded extends the time it takes to complete a reach. There is conflicting evidence, though. Carella et al. (2003) found that participants respond to blindfolding by decreasing mean speed, but also decreasing the total distance of their reach and so maintaining movement time, whilst Sergio and Scott (1998) found that curvature from a straight-line trajectory was greater when blindfolded. These results may differ according to the nature of the task. The dependence of motor performance on vision must be established independently, then, for the task being assessed.

4.1.4 Target distance

If the distance to a target can vary, then it is important to consider the effect this might have on a participant's kinematics. Many studies have found that as target distance increases, movement time, speed (Beggs and Howarth 1972; Fitts 1954; Wadman et al. 1979) and curvature of the trajectory (Boessenkool et al. 1998) also increase. On the other hand Jeannerod (1984) found that, despite increases in distance, movement duration remains invariant. Jeannerod proposed that participants scale the speed of their movement to maintain reach duration.

4.1.5 Trial-on-trial differences

It has previously been shown that reaching kinematics improve with practice (Shuggi et al. 2018). On the other hand, performance could deteriorate due to fatigue or reduced attention over time. For these reasons it is important to account for the number of trials that participants have performed and expect that this effect may differ between patients and health participants.

4.1.6 Inter-individual differences

When performing a group analysis of upper limb performance after hemispherectomy, it should be noted that motor impairments are highly variable. When Wilson (1970) examined sixteen patients at an average of sixteen years post-surgery, eight had no function in the paretic upper limb, whilst seven retained some functional use, being able to steady objects and

hold things placed in the palm. Similarly, Holloway et al. (2000) classified 2/17 subjects they studied as moderately impaired, 2/17 as severely impaired and 13/17 as without upper limb function on the paretic side. Dijkerman et al. (2008) found that one patient out of twelve could produce measurable force on a hand-held dynamometer, 2/12 patients could produce force from the wrist, 7/12 could produce force from the forearm and all patients could exert some force from the upper arm.

Inter-individual differences could bias the results of a group analysis that considered a hemispherectomy group to be homogenous. One solution might be to place participants into homogenous sub-groups, but it is not entirely clear how subjects should be grouped. Bode et al (2005) grouped patients by aetiology before performing analyses of motor function. They found that patients with perinatal stroke perform significantly better than those with either Rasmussen's encephalitis or cortical dysplasia. Both Holloway (2000) and Choi et al. (2007) also found that patients with Rasmussen's perform worse than those who have suffered a stroke, but no significant differences were found for those with cortical dysplasia. Both Jonas et al. (2004) and van der Kolk et al. (2012) found that those with cortical dysplasia have similar outcomes to those with cerebral infarction.

The difficulty in finding clear sub-group differences may be due to small sample sizes and variability within the sub-groups. Of the 13/17 subjects that Holloway et al. classified as having no function in the paretic upper limb, three had suffered cerebral infarction. In the study by Choi et al., mean upper limb scores were ranked in descending order: cortical dysplasia (M = 36, *range* = 33-39, n = 2), stroke (M = 33.6, *range* = 26-38, n = 5) and Rasmussen's (M = 23.8, *range*: 22-30, n = 5). There was, then, a wide range of scores within each small sized sub-group. It is clear that whilst there has been consistent evidence that as a group Rasmussen's patients have worse outcomes than other aetiology groups, classification by aetiology is only a rough guide, and there remains great inter-individual variability not only in the population of hemispherectomised patients but also within the aetiology sub-groups.

It is important, then, to account for the inter-individual differences of hemispherectomised patients. The need may be even more pressing when analysing the kinematics of an unconstrained movement. When performing an unconstrained action, there are many possible trajectories that are consistent with the task requirements. It may be unsurprising, therefore, that there is significant inter-individual variability in the reach trajectories of healthy participants. Jeannerod (1984) found that the mean movement duration for a self-paced reaching action varied from 674 ms for one subject up to 1013 ms for another, whilst peak speed ranged from 560 mm/s up to 820 mm/s. Boessenkool et al. (1998) found that, for a self-paced reaching movement, some healthy participants chose trajectories that curved toward their midline, some curved away, whilst others produced a sinusoidal movement. For this reason, both Jeannerod and Boessenkool et al. chose not to average across subjects but instead report individual values.

There may be many causes of inter-individual differences, including biomechanical differences, differences in neuronal properties and levels of arousal and motivation. For example, Sabes et al. (1998) showed that, when subjects reach around an obstacle, the spatial trajectory of the reach can be predicted from the inertial properties of the arm, which differ between participants. Motor performance differences are also related to measurable properties of the neural pathways involved. Between-subject differences in the diffusivity values (fractional anisotropy) of the corpus callosum – a pathway providing interhemispheric transfer of information – correlate with inter-individual differences in bimanual coordination (Johansen-Berg et al. 2007).

If it is important to account for inter-individual differences in the kinematics and motor performance of healthy participants, then it could be more so when participants have significantly different levels of motor disability. Domellöf et al. (2009) showed that the kinematic properties of patients with unilateral cerebral palsy vary according to the level of impairment: patients with unilateral cerebral palsy and moderate hemiplegia have lower curvature and number of movement units than those with severe hemiplegia. Measures

of spread also reveal the variability of inter-individual performance. Hermsdörfer (1999b) analysed the prehension kinematics of the non-paretic upper limb of patients with unilateral adult stroke. Whilst they showed that the peak speed of patients with a left-sided lesion (*M* = 855 mm/s, *SD* = 153 mm/s) was significantly lower than a left-handed healthy group (*M* = 1001 mm/s, *SD* = 173 mm/s), data from both groups were widely spread.

It is possible to choose a method of statistical analysis that measures and accounts for inter-individual differences (see Appendix 2 for more detail). A standard regression model explains the value of one variable in terms of explanatory, fixed effects. A model that includes both standard fixed effects and random effects is termed a mixed effects model. Random effects terms can group the observations by subject, allowing a different intercept and/or coefficient for each subject. If, for example, a treatment condition had the same effect on all subjects, but each subject started from a different baseline, a random intercept term could be included. The effects may not, however, have been consistent over all participants. In fact, one clear danger with estimating the mean effect is that if, for example, three participants have a positive slope and three have an equivalent slope in the negative direction, the mean effect would be zero. A random slope term could then be used that allows the slopes to vary by subject. Based on these considerations, in the current analysis the explained variables will be estimated with a simple fixed effects model, then a fixed effects and random intercepts mixed model and lastly a fixed effects, random intercepts and random slopes mixed model. Each model will then be evaluated and the best model will be selected. In order to provide insight into inter-individual differences, rather than just group effects, the intercepts and slopes of each patient will be presented.

4.2 Methodology

4.2.1 Data acquisition

Given the lack of studies in this area, a new motor task was created that was appropriate for the cohort. The motor task was designed to meet various requirements. Firstly, the action needed to be one that all patients could perform with their paretic arm and hand. It could not, therefore, require highly skilled or forceful movement or independent use of the fingers. Secondly to satisfy the aims of the study, the action needed to be one that could be performed under varying conditions. Specifically, it had to be one that could be performed by the non-paretic arm, paretic arm or bimanually, with visual feedback or blindfolded. Thirdly, to ensure that the assessment was relevant to daily living, it was preferred that the action was one that may often be performed in a normal day. Based on these requirements it was decided that the action of reaching to and pressing a soap dispenser was appropriate.

The materials then needed to be arranged in a format that would not introduce bias. Firstly, if the participant was seated in an uncomfortable or unstable position this could bias task performance. For this reason, the height and position of the table and chair were set to ensure comfort and stability. Secondly, since only upper limb movement was being recorded, not movement of the trunk, it was desirable to limit trunk movement. It was also, however, desirable for the task to resemble a normal environment. For these reasons the table was positioned close to the body to limit trunk movement. Thirdly, as each participant's body dimensions varied, if the materials were placed in the same absolute positions this could cause a disadvantage for some participants. For this reason, the materials were placed and adjusted relative to the participant's dimensions.

Based on these requirements, the following task was used (see Figure 13). Each participant was seated in a high-backed chair with a table in front, pushed in closely but comfortably against the participant's abdomen. The table and chair were adjusted so that the participant's knees were bent at a right angle with feet flat on the floor and the forearms resting comfortably on

the table with elbows bent at a right angle. The participant was asked to place both forearms on the table with hands directly in front of the shoulders and one position-marker (a small adhesive Velcro marker) was placed beneath each finger middle finger. The texture of the Velcro enabled participants to locate the position-markers when blindfolded. Since hemispherectomised patients have impaired cutaneous sensation, patients practised locating the marker when blindfolded before the experiment began. An empty, but weighted, soap dispenser (a standing, plastic pump bottle) was placed on the table in front of the participant, at the midpoint between these position-markers. The participant was then asked to tuck each arm in against the abdomen, in turn, and a position marker was placed beneath each middle finger. Since the soap dispenser was positioned relative to the size of the participant's body, the straight-line-distances between the position-markers and the soap dispenser (the target distance) varied between participants.

Each participant was required to press the empty soap dispenser with either the dominant or non-dominant hand. They were instructed to perform the action at a natural speed using arms and hands only, not the trunk. They were instructed to press the soap dispenser with the centre of the palm, not the fingers. For each block of trials, the participant was told that the experimenter would count to twelve. The participant was instructed to wait for each count, then press the dispenser with the indicated hand, return their hand to the same position-marker on the table and wait for the next count. The participant began each trial with the middle finger of the pressing hand placed on the position marker closest to the body. The middle finger of the other hand was placed on the position marker directly in front of its shoulder.

The conditions were not counterbalanced or randomised. Counterbalancing or randomisation would have been a convenient method of controlling for the repeated measures experimental design, however one of the goals was to analyse differences between individuals, which meant both approaches would have created a new set of problems. If the order of the conditions had varied between members of the comparison group then, for consistency, they

should also have varied between members of the patient group. But this would make testing for inter-individual differences problematic, since patients would have been tested in different condition orders, which is effectively to say that they would have been tested under different conditions. This is a significant problem with repeated measures designs – effects of one trial on the next are present after counter-balancing or randomisation, but are less predictable and vary between participants. Instead, the repeated measures experimental design was accounted for with a linear mixed effects model. To control for time-varying effects such as fatigue, practice or attention, a factor was included in the statistical model that indexed the trial number. Values were estimated after controlling for the effect of trial-index. This approach has been used in previous studies to take the effects of trial order under statistical control rather than making those effects less predictable through counter-balancing or randomisation (Baayen et al. 2008).

Participants were invited to perform the task whilst their movements were recorded with optical motion capture. During each session, motion of the upper limbs was recorded at 300Hz using either a calibrated six or eight camera Oqus motion-capture system and Qualisys Track Manager (QTM) 2.9 software (Qualisys AB, Sweden). To track motion of the forearms, clusters of four retro-reflective markers were attached to rigid bodies (sheets of aluminium alloy, sandwiched between two layers of non-reflective closed-cell foam) and these rigid bodies were attached to and shaped around the dorsum of each forearm just proximal to the wrist. Participants repeated the task under eight conditions, separated into 16 blocks with 12 trials per block (see Table 5). One continuous motion capture recording was made for each block. If the participant made an error, by either beginning the movement before the experimenter counted the trial, or stopping during the reach (e.g. if they were confused as to which hand was the pressing hand for this trial) the trial was marked for exclusion. The maximum number of trials excluded for any participant across both iterations of a single condition was 3, i.e. there were at least 21 trials for each condition per participant.

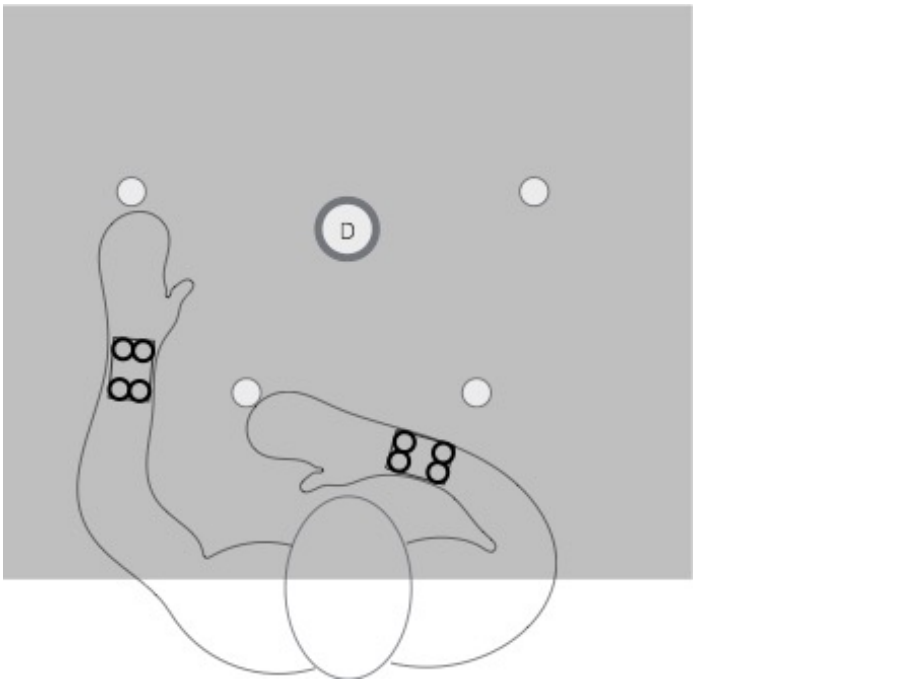

Figure 13. Motor task setup

Four retro-reflective markers (see circles with black outlines in top image) were attached to rigid, marker holders, which were then attached to the forearm just proximal to the wrist. The four white circles indicate position markers. At the beginning of each trial one arm was tucked in against the body, with the middle finger on a position marker, whilst the other was directed forward with the middle finger on a position marker. On cue, the participants pressed the dispenser (marked 'D' in the diagram) with the hand that began close to the body (in this example, the right hand). For a bimanual trial, the participant also placed the other hand beneath the dispenser. This action is depicted in the bottom image.

Table 5. Order of testing

Values indicate block number of the corresponding combination of conditions. Twelve trials were recorded per block.

		Vision		*Blindfolded*	
		Dominant	*Non-dominant*	*Dominant*	*Non-dominant*
Unimanual	*1st Iteration*	1	2	3	4
	2nd Iteration	5	6	7	8
Bimanual	*1st Iteration*	9	10	11	12
	2nd Iteration	13	14	15	16

4.2.2 Data processing

For each marker trajectory, the representation was identified manually in QTM. A small proportion of missing marker data were interpolated with a maximum gap fill of 30 frames using QTM's inbuilt cubic spline interpolation. Each forearm cluster of four markers was defined as a rigid body. The visual reconstruction of all trajectories was quality checked by the experimenter for abnormal paths due to mislabelled markers. If mislabelled markers were identified they were relabelled and the rigid bodies were redefined. For each block, event markers were added manually at the start and end of each trial, excluding any trials marked for removal. The event markers and 3D position data of the rigid bodies were exported to Matlab for all further processing (MATLAB R2015a, The MathWorks Inc., Natick, MA).

Blocks were segmented into trials based on the event markers (see Figure 14 for raw data from comparison and patient participants). The methods of collecting and processing kinematic data can introduce high-frequency noise in the spatial signal. This is particularly problematic after differentiation. To attenuate noise a low-pass filter (4^{th} order two-way Butterworth filter with a low-pass cut-off at 20Hz) was applied to the position data. 20Hz was selected to exclude high frequency noise but pass true forearm movement.

Butterworth filters are optimally flat in the pass-band and so appropriate for preserving the true signal of human motion. The filter was applied two-ways to avoid phase-shift, resulting in a 4th order filter. This selection of filter parameters is commonly used in kinematic studies of hemiparetic patients performing reaching tasks (Cirstea and Levin 2000; Kantak et al. 2016; Mandon et al. 2016; Michaelsen et al. 2001; Rose and Winstein 2005).

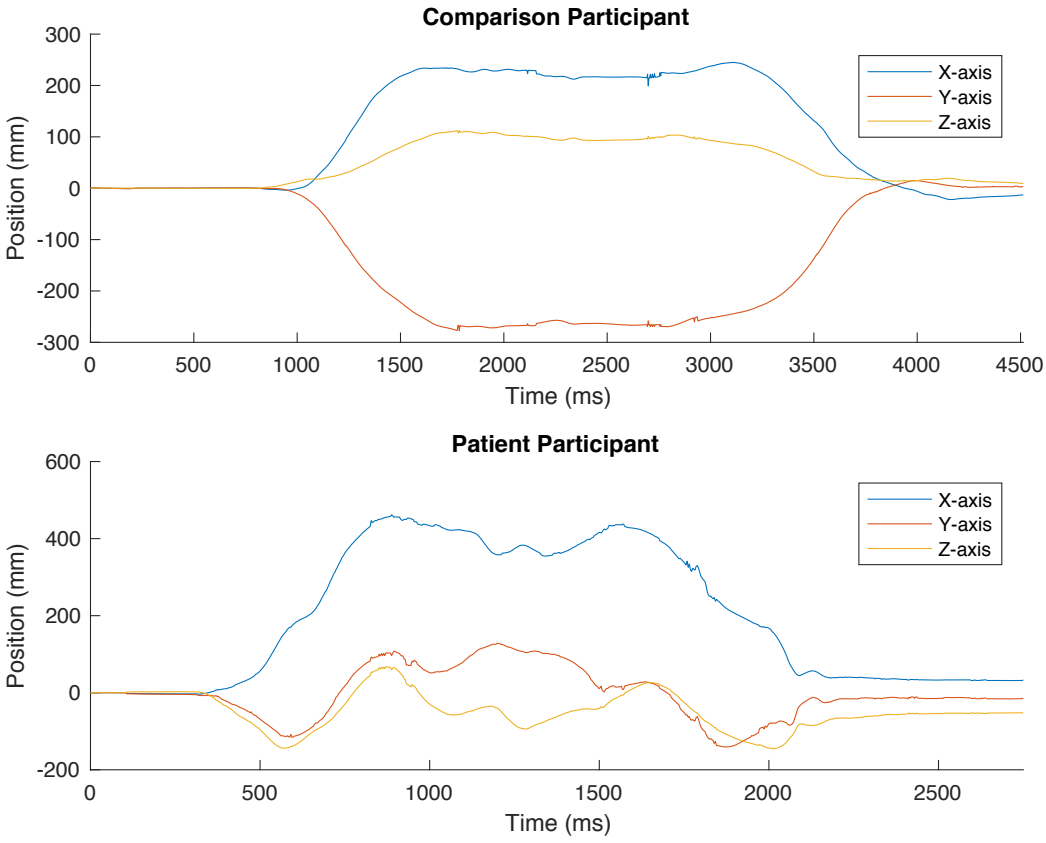

Figure 14. Raw position data from a trial

These plots represent the forearm position along all three axes as participants pressed a soap dispenser and returned their arm to the table (raw data). In these examples, participants used their non-dominant arm and visual feedback was available, the comparison participant reaching with the left arm and the patient participant reaching with the right arm, which was the paretic arm.

An alternative approach to remove noise from the data is to use a smoothing spline, where the data is split into pieces and a polynomial is fitted to each piece (Winter 2009). The smoothness of the total trajectory can be defined in terms of a smoothing parameter – a value between 0 and 1, where 0 is a closer fit to the data and 1 is a smoother trajectory. This approach was also investigated. The smoothing parameter of the cubic smoothing spline was set to .03. This parameter was selected through trial and error, by visually checking that the spline reflected the underlying trend in the data whilst removing noise.

The smoothed data were visually compared to the filtered data by plotting (see Figure 15). With a smoothing parameter of .03, the filtered and smoothed data were similar. The Butterworth filter was used for all further analysis rather than the cubic smoothing spline, since this approach is more common in kinematic studies of hemiparetic studies. Velocity was defined as the first derivative of the filtered 3D position data. Speed was defined as the magnitude of the filtered 3D velocity.

For each trial, reach onset and end were identified for the pressing arm and, for bimanual trials, for the receiving arm too. For each arm, the reach phase of each arm was considered to have begun once the arm had left the table. The reach phase of the pressing arm was considered to have ended when the palm of the pressing hand first contacted the dispenser. The reach phase of the receiving arm was considered to have ended when the receiving hand was first below the spout of the dispenser. There were no direct measures of when these events occurred (for a discussion of this problem see the discussion of this chapter). Instead the positions were approximated by estimating when the forearm first left the vicinity of its start position (the start zone) and came within the vicinity of the position it would hold during the pressing/receiving action (the target zone).

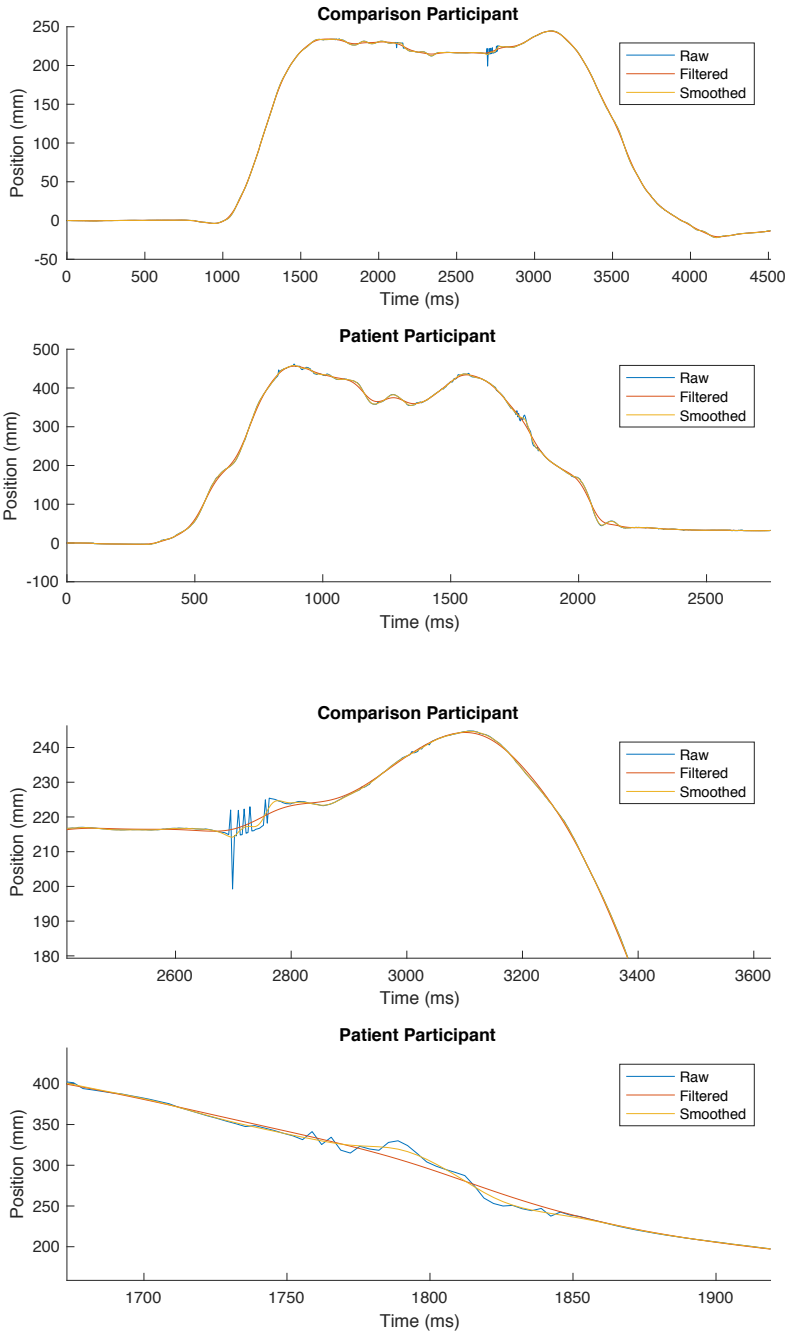

Figure 15. Raw, filtered and smoothed position data from a trial

Top two plots: X-axis position of the forearm. Bottom two plots: same data, but zoomed in. Noise was present that would have been amplified when calculating velocity. Two methods were tested to attenuate the noise: (1) 4th order two-way Butterworth filter with low-pass cut-off at 20Hz ('Filtered'); (2) spline with smoothing parameter of .03 ('Smoothed).

Reach onset was found by: (1) finding the first frame at which the distance from the first frame exceeded 15% of the maximum distance travelled within that trial – at this frame the forearm was considered to have left the start zone; (2) finding the previous frame where speed was below 5cm/s – at this frame the forearm was considered to have started moving. A speed threshold of 5cm/s has been used in previous kinematic studies of hemiparetic patients (Artilheiro et al. 2014; Kukke et al. 2016; Mandon et al. 2016; Robertson et al. 2009). Other studies have used 5% of maximum speed (Camerota et al. 2014; Formica et al. 2012), though in the current task 5cm/s approximated this value: across all trials of all participants, 5cm/s was on average 3.48% of maximum speed (*S.D.* = 1.07). Reach end was found by: (1) finding the first frame at which the distance from the first frame exceeded 85% of the maximum distance travelled within that trial – at this frame the spline was considered to have entered the target zone; (2) finding the next frame at which the speed was below 5cm/s – at this frame the forearm was considered to have stopped moving. Every trial was visually inspected to ensure that reach onset and end had been accurately identified (see Figure 16). This method meant that the position at reach onset and end, and therefore the straight-line-distance, varied between trials.

For each trial, the values of the explained variables were derived: movement time, average speed, maximum speed, length index, number of movement units and the covariate straight-line-distance. The straight-line-distance was defined as the Euclidean distance between the coordinates at reach onset and reach end. For each bimanual trial, the explained variables onset lag, end lag, number of sequential movements and bimanual movement time were also derived.

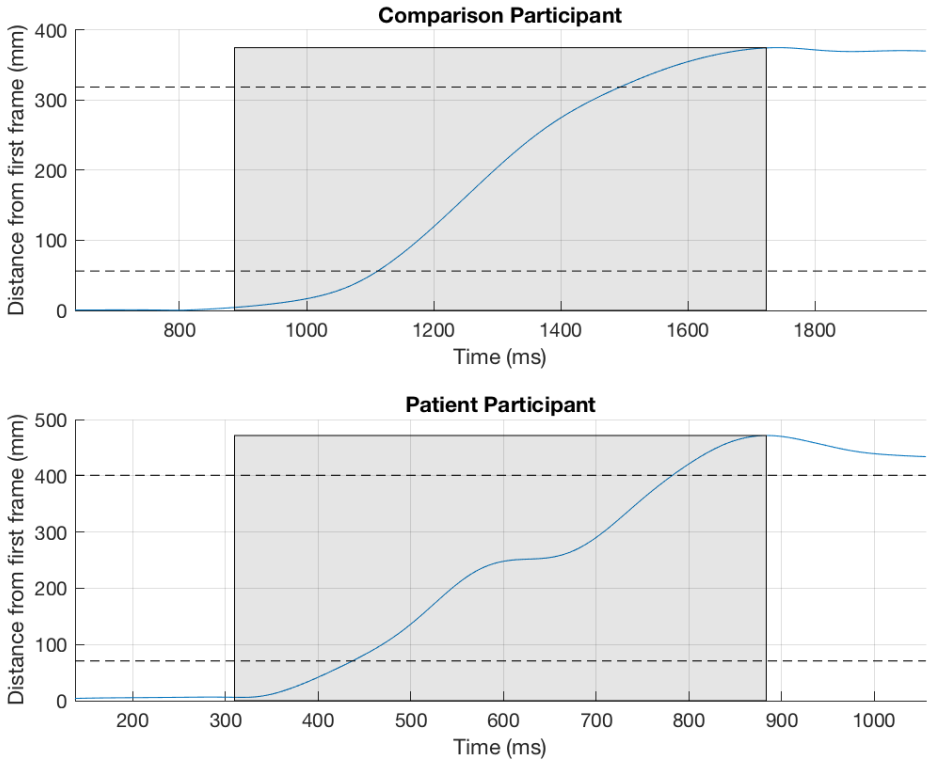

Figure 16. Estimating reach onset and end

These plots represent the forearm's distance to the first frame. Reach onset was estimated by first finding the frame at which 15% of the distance travelled from the first frame was first crossed (bottom dashed line) and then find the preceding frame where speed was < 5cm/s. Similarly, reach end was estimated by first finding the frame at which 85% of the distance travelled was first crossed (top dashed line) and then find the next frame where speed was < 5cm/s. In each plot the shaded area represents a reach phase.

The shape of a participant's trajectory was characterised by the length index. The length index was defined as the ratio of the three-dimensional length of the reach trajectory to the straight-line distance. For an ideal straight line, the length index is 1 whilst for a half-circle it is 1.57. The length index is related to the maximal perpendicular distance between the straight line and the true path, as has been used in other studies (Atkeson and Hollerbach 1985) or the distance to the straight-line at 50% of movement time (Miall and Haggard 1995; Wolpert et al. 1994). The length index was preferred to these methods

for two reasons: firstly, it is commonly used in kinematic studies of hemiparetic patients (Cabral-Sequeira et al. 2016; de Oliveira Cacho et al. 2015; Mandon et al. 2016); secondly, some participants produced S-shaped instead of arced trajectories, which intersected the straight-line.

The temporal segmentation of the reach was analysed in terms of the number of movement units. The simplest definition of a movement unit is an acceleration phase followed by a deceleration phase. This is the definition reported in many kinematic studies of hemiparetic patients (Chen et al. 2014; de Oliveira Cacho et al. 2015; Mottet et al. 2017), however, an acceleration-deceleration phase can be caused by measurement error, rather than a distinct unit of action, hence additional criteria were used. The parameters were used on the basis that they have been used in previous kinematic studies of hemiparetic patients (Alt Murphy et al. 2011; 2012; 2013; Bustrén et al. 2017). These studies have not used an objective rule for selecting the parameters, rather they have been selected on an empirical basis after visual monitoring of the trajectories. The criteria were: (1) small inflexions in the speed profile were ignored by setting a minimum peak prominence of 20mm/s, i.e. peaks were guaranteed to have a vertical drop of more than 20mm/s from the peak on both sides without encountering either the end of the signal or a larger intervening peak; (2) multiple movement units that occurred in quick succession were ignored by setting a minimum time between two subsequent peaks of 150ms; (3) short duration units were ignored by setting a minimum width of 45ms. The width was defined as the time from crossing 50% of the peak prominence during the acceleration phase to crossing 50% of the peak prominence during the deceleration phase (see Figure 17).

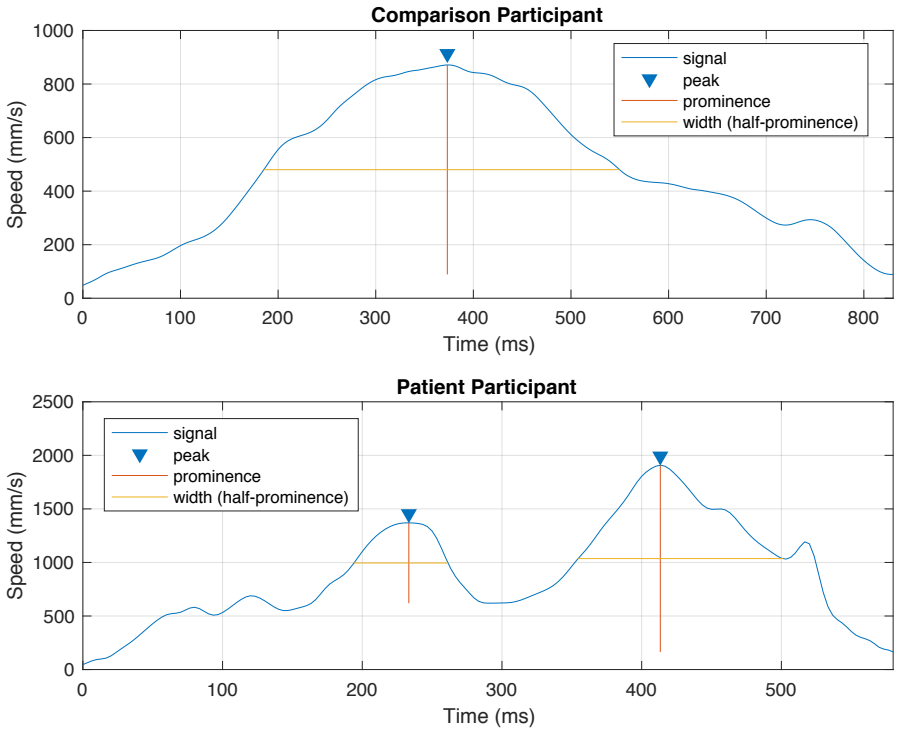

Figure 17. Definition of a movement unit

A movement unit was defined as an acceleration phase followed by a deceleration phase. Short acceleration-deceleration phases can be seen in the plot that are unlikely to reflect controlled movement, such as at around 120ms in the Patient Participant plot. These phases were ignored by using the following criteria: (1) small inflexions in the speed profile were ignored by setting a minimum peak prominence of 20 mm/s, i.e. peaks were guaranteed to have a vertical drop of more than 20 mm/s from the peak on both sides without encountering either the end of the signal or a larger intervening peak; (2) multiple movement units that occurred in quick succession were ignored by setting a minimum time between two subsequent peaks of 150 ms; (3) short duration units were ignored by setting a minimum width of 45 ms. The width was defined as the time from crossing 50% of the peak prominence during the acceleration phase to crossing 50% of the peak prominence during the deceleration phase. These parameters have been used in previous kinematic studies of hemiparetic patients (Alt Murphy et al. 2011; 2012; 2013; Bustrén et al. 2017).

For bimanual trials, onset lag was defined as the absolute difference between the pressing arm reach onset and the receiving arm reach onset, in milliseconds. End lag was defined as the absolute difference between the pressing arm reach end and the receiving arm reach end, in milliseconds. For each participant, the number of sequential movements was defined as the number of bimanual trials for which reach end of either arm preceded reach onset of the other arm. This does not preclude the possibility that a participant could break the reach to the dispenser into distinct stages for each arm, e.g. reach half-way to the dispenser with the left arm and stop moving, reach halfway with the right arm and stop moving, complete the left arm reach, then complete the right arm reach. For this reason, the percent of the reach phase where the speed of both arms was above 5cm/s was calculated, referred to as ‘bimanual movement time’.

4.2.3 Statistical analysis

The theoretical reasoning behind the statistical methodology applied here is given in Appendix 2. Each explained variable was modelled with regression analysis. The fixed effects terms of the regression models included the straight-line-distance (since the straight-line-distance between movement onset and end was allowed to vary), trial-index (trial number as a percentage of all trials in all blocks of the session, to test for trial-by-trial differences) and dummy variables that referred to the participant group and condition under which each trial was performed: group (comparison/patient), manuality (bimanual/unimanual), feedback (vision/blindfolded) and pressing-hand (the hand that pressed the dispenser, either the participant's dominant or non-dominant). If the participant was a patient then, where it is not explicitly mentioned, 'dominant' refers to the non-paretic hand whist 'non-dominant' refers to the paretic hand. For unimanual trials, 'pressing hand' referred simply to the hand that was engaged in the task. For bimanual trials, since both hands were engaged in the task, the hand referred to by 'pressing hand' pressed the dispenser whilst the other hand was placed beneath the spout of the dispenser.

Standard linear regression assumes the data are a random sample of independent observations. This assumption had been violated since repeated measures were taken from the same subject: each of the 18 subjects was tested under every condition. A random effects term (1|Subject) was therefore entered into the model, allowing the intercept to vary independently for each subject. For each subject, correlation between observations was assumed to be constant and hence a compound symmetry covariance structure was used for the random effects. This assumption was tested through diagnostic plots of the residuals. With this approach, individual intercepts were estimated for each participant. In case of individual variation in the estimated coefficients of the model, random slopes were also included for Group:PressingHand, Group:Feedback and Group:Manuality.

For each explained variable (*y*), except onset and end lag (for which *Manuality*, *Group:Manuality* and *Group:Manuality:PressingHand* were excluded, with *Manuality* also excluded from the random effects term), the formula for model specification was, in Wilkinson notation (where ':' indicates an interaction):

> *'y ~ 1 + StraightLineDistance + PressingHand + Feedback + Manuality + TrialIndex + Group + Group:PressingHand + Group:Feedback + Group:Manuality + Group:TrialIndex + Group : PressingHand : Manuality + (1|Subject) + (Group:PressingHand-1|Subject) + (Group:Feedback-1|Subject) + (Group:Manuality-1|Subject)'*

All models were fitted with a reference-coding scheme for the dummy variables (i.e. with the coefficient for the first category set to zero). The reference values were set as: group = comparison group; pressing-hand = dominant; feedback = vision; manuality = unimanual (except for onset and end lag, where manuality was excluded).

Models were initially fit with all observations included. However, the results could have been biased by outliers and/or sequential reaches. For example, if a participant reaches more slowly when moving both arms simultaneously, this difference would not be apparent if the bimanual reach was performed as sequential unimanual reaches. For this reason, each model was refitted with outliers excluded, sequential reaches excluded and both outliers and sequential reaches excluded. An outlier was defined as a standardised residual whose value was $> Q_3 + (1.5 \times (Q_3 - Q_1))$ or $< Q_1 - (1.5 \times (Q_3 - Q_1))$, where Q_1 and Q_3 are the first and third quartiles of the set of standardised residuals, respectively. The full set of fixed effect regression estimates are reported with and without outliers. If the significance of any fixed effect moved above or below the .05 threshold when sequential reaches were excluded, this is reported in the text.

4.2.4 Model diagnostics

All explained variables were fitted with linear mixed effects modelling, except the number of movement units which was fitted with a generalised linear mixed effects model, specifying a Poisson distribution with a log link function. The linear mixed effects models were fitted with maximum likelihood (ML) estimation. The generalised linear mixed effects model was fitted with ML using Laplace approximation (the models would later be compared with likelihood ratio tests and, unlike some fitting methods such as maximum-pseudo-likelihood, statisticians have considered Laplace approximation as appropriate for likelihood ratio tests when data has been fitted with generalised linear mixed effects modelling (Bolker et al. 2009)). To informally test if any of the regression assumptions had been violated, three plots were generated for each model: (1) a histogram of the Pearson residuals, (2) the Pearson residuals versus the fitted values and (3) the Pearson residuals at *t* against the lagged Pearson residuals at *t*-1. All diagnostic plots can be found in Appendix 3.

To assess the contribution of the random effects terms to the model, each model was fitted first with fixed effects only (fixed effects model), second with fixed effects and the random intercepts (random intercepts model) and thirdly with random intercepts and slopes (random slopes and intercepts model). The best model was selected by the following criteria (see Figure 18). The fit of the fixed effects only model was compared to the random intercepts model with a likelihood ratio test. If, when considering the extra degrees of freedom, the random intercepts model did not explain a significantly greater proportion of the variance than the fixed effects only model, then the fixed effects only model was compared to the random intercepts and slopes model. The better of these two models was then chosen by the same criteria. If, however, the random intercepts model was considered better than the fixed effects only model, then the random intercepts model was compared to the random intercepts and slopes model with the same method and the better of the two models was chosen by the same criteria.

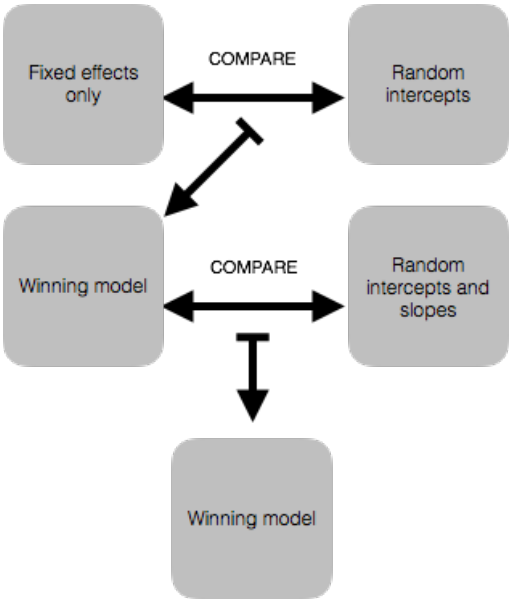

Figure 18. Selecting model terms

For all explained variables, the mixed effects model with random intercepts provided a better fit than fixed effects only, except for number of movement units (Table 6). For this variable, the random intercepts and slopes model was better than the fixed effects only model. For all other explained variables, the model with random intercepts and slopes was a better fit than the random intercepts model. The overall fit of each model is reported in terms of the *adjusted* R^2 value. All models provided good fits to the data (*adjusted* R^2 >= .5), except for length index and number of movement units. This indicates that, for these variables, the estimated effects may be inaccurate and should therefore be approached with some caution.

Table 6. Model selection

Each pair of models was compared with likelihood ratio tests (pairs indicated by shading). DF = free parameters in model; LRStat = likelihood ratio test statistic, comparing model in current row to model in row above; pValue = p-value for simulated likelihood ratio test; Adj. R^2 = adjusted R^2

Explained variable	*Model*	*DF*	*LRStat*	*pValue*	*Adj. R^2*
Movement time	Fixed effects	13			0.29
	Random intercepts	14	1646	<.001	0.57
	Random intercepts	14			0.57
	Random intercepts and slopes	17	241	<.001	0.61
Average speed	Fixed effects	13			0.34
	Random intercepts	14	2114	<.001	0.65
	Random intercepts	14			0.65
	Random intercepts and slopes	17	378	<.001	0.69
Maximum speed	Fixed effects	13			0.45
	Random intercepts	14	1870	<.001	0.69
	Random intercepts	14			0.69
	Random intercepts and slopes	17	519	<.001	0.74
Length index	Fixed effects	13			0.1
	Random intercepts	14	1307	<.001	0.4
	Random intercepts	14			0.4
	Random intercepts and slopes	17	200	<.001	0.45
Number of movement units	Fixed effects	12			0.24
	Random intercepts	13		1	0.24
	Fixed effects	12			0.24
	Random intercepts and slopes	16	8.63	0.071	0.25
Onset lag	Fixed effects	10			0.23
	Random intercepts	11	779	<.001	0.53
	Random intercepts	11			0.53
	Random intercepts and slopes	13	277	<.001	0.6
End lag	Fixed effects	10			0.16
	Random intercepts	11	390	<.001	0.35
	Random intercepts	11			0.35
	Random intercepts and slopes	13	404	<.001	0.5

4.3 Results

4.3.1 Movement time

Summary statistics are presented in Figure 19. Estimates from the regression model are presented in Table 7. Increases in the distance between reach onset and end predicted a significant increase in movement time. Under the reference condition, the difference between the groups was not a significant predictor of movement time, nor was the effect of blindfolding or trial index. When pressing with the non-dominant hand, the comparison group were estimated to take significantly less time to complete a trial than when pressing with the dominant hand, although the difference was small. In contrast, the patient group were estimated to take significantly and substantially longer to complete a reach with the paretic hand than the non-paretic. Movement time of the comparison group under the reference condition was estimated to be significantly greater for bimanual trials than unimanual trials. The estimate for the patient group when pressing with the non-paretic hand during bimanual trials was not significantly different to this, but when pressing with the paretic hand bimanual reaching took even longer.

Excluding sequential reaches did not affect these conclusions. 94 trials (2.73%) were identified as outliers. This included 21 comparison group trials (0.91%) and 73 patient group trials (6.38%). With outliers excluded, the interaction between group and trial index was found to be a significant predictor of movement time (Table 7). This indicated that with outliers excluded the patient group - unlike the comparison group - reduced movement time over the course of a session.

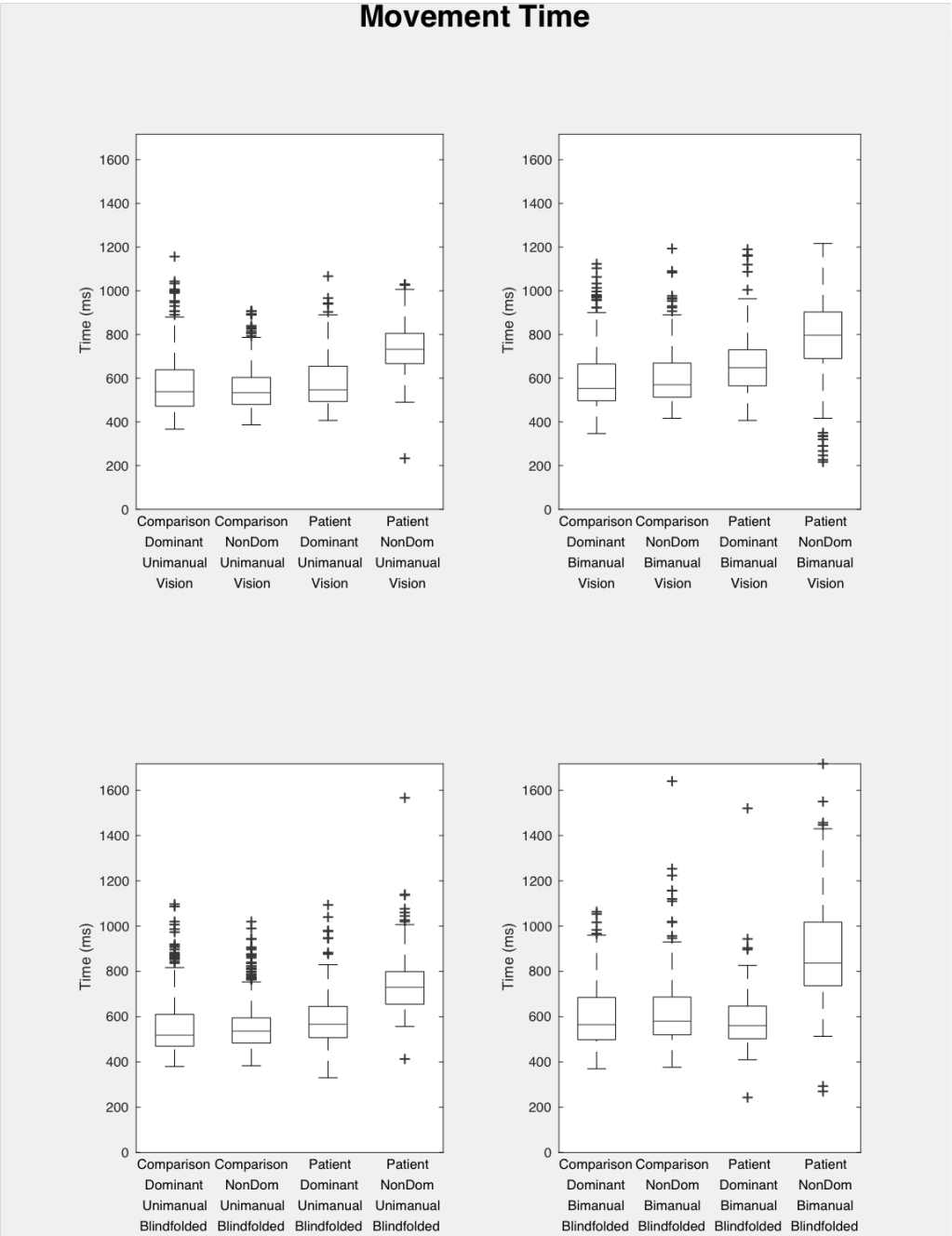

Figure 19. Movement time box-plots

On each box, central mark is median, edges of box are 25th and 75th percentiles, whiskers extend to most extreme datapoints algorithm considers to be not outliers, and outliers are plotted individually. Points are outliers if they larger than Q3+1.5(Q3-Q1) or smaller than Q1-1.5*(Q3-Q1), where Q1 and Q3 are the 25th and 75th percentiles, respectively.*

Table 7. Movement time regression estimates

Top, estimates with outliers included. Bottom, estimates with outliers excluded. For definition of an outlier see Statistical Analysis section. Estimate = estimated coefficient; SE = standard error of coefficient; tStat = t-statistic; DF = degrees of freedom for t-test; pValue = p-value for t-test.

	Estimate	SE	tStat	DF	pValue
(Intercept)	367	31.9	11.5	3434	<.001
TrialIndex	-4.78	17.3	-0.276	3434	.783
Group_Patient	12.6	51.5	0.245	3434	.807
Manuality_Bimanual	44.6	9.7	4.6	3434	<.001
PressingHand_NonDom	-26.4	4.85	-5.45	3434	<.001
Feedback_Blindfolded	-0.981	4.9	-0.2	3434	.841
StraightLineDistance	0.608	0.0367	16.6	3434	<.001
TrialIndex: Group_Patient	-24.3	29.6	-0.82	3434	.412
Group_Patient: Manuality_Bimanual	13.8	33.3	0.415	3434	.678
Group_Patient: PressingHand_NonDom	141	31.4	4.47	3434	<.001
Group_Patient: Feedback_Blindfolded	14.9	20.1	0.742	3434	.458
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	52	12.4	4.19	3434	<.001

	Estimate	SE	tStat	DF	pValue
(Intercept)	402	28.8	13.9	3340	<.001
TrialIndex	2.05	14.4	0.142	3340	.887
Group_Patient	28.6	47	0.609	3340	.543
Manuality_Bimanual	37.6	8.1	4.65	3340	<.001
PressingHand_NonDom	-22.8	4.05	-5.62	3340	<.001
Feedback_Blindfolded	-2.26	4.09	-0.551	3340	.582
StraightLineDistance	0.495	0.0311	15.9	3340	<.001
TrialIndex: Group_Patient	-57.9	25.2	-2.3	3340	.022
Group_Patient: Manuality_Bimanual	26.5	23.2	1.14	3340	.253
Group_Patient: PressingHand_NonDom	134	27.9	4.79	3340	<.001
Group_Patient: Feedback_Blindfolded	0.353	15.9	0.0222	3340	.982
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	4.47	10.9	0.412	3340	.681

4.3.2 Average speed

Summary statistics are presented in Figure 20. Estimates from the regression model are presented in Table 8. Increases in straight-line distance were a significant predictor of increases in average speed. Under the reference condition, the difference between the groups was not a significant predictor of average speed, nor was blindfolding. Average speed was significantly predicted by trial index though, decreasing over a session. The effect on the patient group was estimated to be the opposite, with a substantial increase over a session. When pressing with the non-dominant hand, the comparison group were estimated to be slightly faster than when pressing with the dominant. In contrast, the patient group were estimated to be substantially slower when reaching with the paretic hand. The difference between bimanual and unimanual trials was not a significant predictor of average speed for the comparison group under the reference condition. This was also true for the non-paretic hand of the patient group, but when pressing the paretic hand was estimated to have significantly lower average speed during bimanual reaching.

Excluding sequential reaches did not affect these conclusions. 10 trials (0.29%) were identified as outliers. This included 10 comparison group trials (0.43%) and 0 patient group trials. The same conclusions were found when these trials were excluded from the model (Table 8).

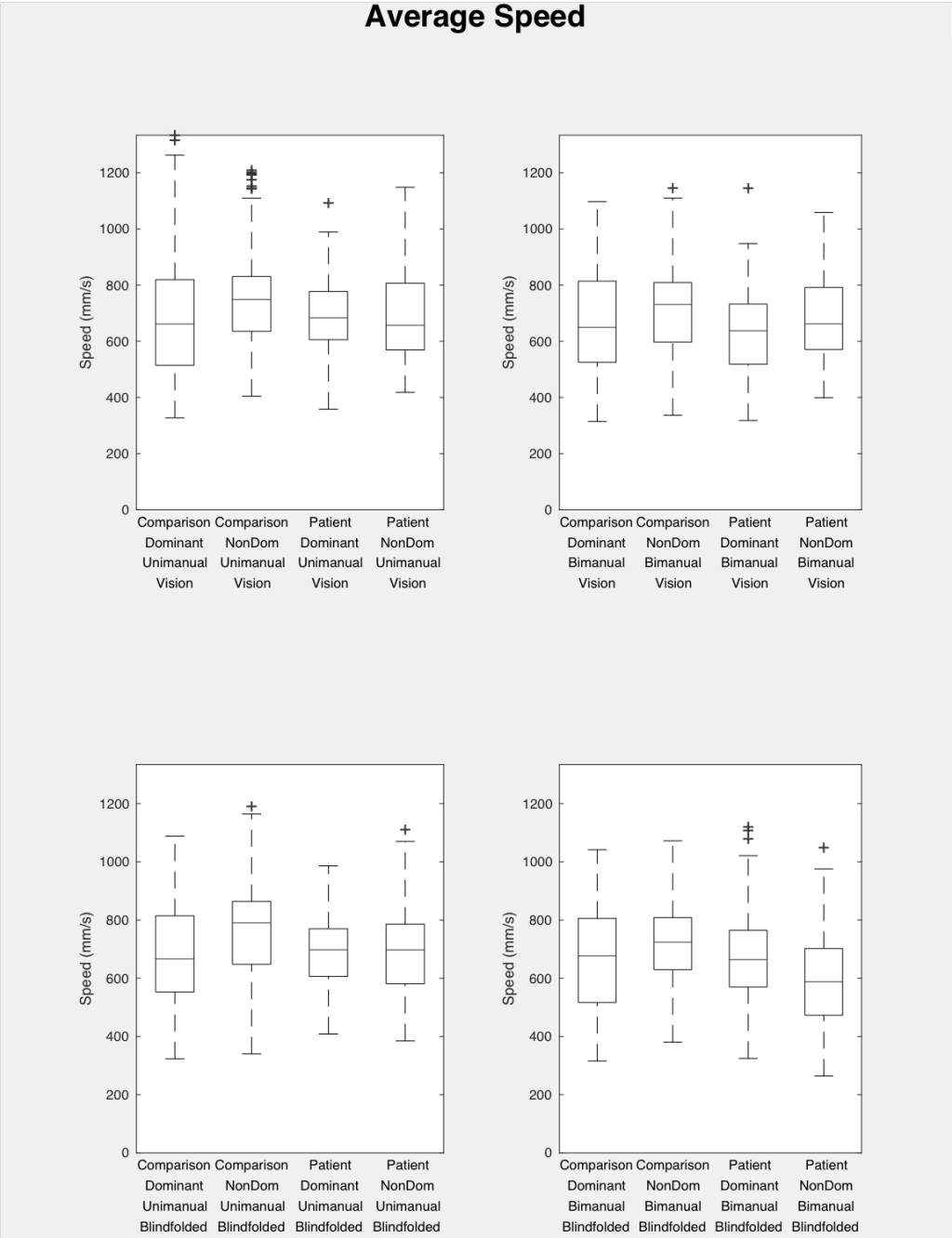

Figure 20. Average speed box-plots

On each box, central mark is median, edges of box are 25th and 75th percentiles, whiskers extend to most extreme datapoints algorithm considers to be not outliers, and outliers are plotted individually. Points are outliers if they larger than Q3+1.5(Q3-Q1) or smaller than Q1-1.5*(Q3-Q1), where Q1 and Q3 are the 25th and 75th percentiles, respectively.*

Table 8. Average speed regression estimates

Top, estimates with outliers included. Bottom, estimates with outliers excluded. For definition of an outlier see Statistical Analysis section. Estimate = estimated coefficient; SE = standard error of coefficient; tStat = t-statistic; DF = degrees of freedom for t-test; pValue = p-value for t-test

	Estimate	SE	tStat	DF	pValue
(Intercept)	338	31.6	10.7	3434	<.001
TrialIndex	-34.6	15.2	-2.27	3434	.023
Group_Patient	-41.7	51.8	-0.804	3434	.422
Manuality_Bimanual	-5.54	8.54	-0.649	3434	.517
PressingHand_NonDom	11	4.27	2.56	3434	.010
Feedback_Blindfolded	-4.64	4.32	-1.07	3434	.283
StraightLineDistance	1.09	0.0324	33.7	3434	<.001
TrialIndex: Group_Patient	102	26.1	3.9	3434	<.001
Group_Patient: Manuality_Bimanual	-56.5	36.1	-1.57	3434	.117
Group_Patient: PressingHand_NonDom	-73.5	32.1	-2.29	3434	.022
Group_Patient: Feedback_Blindfolded	-13.3	20.9	-0.639	3434	.523
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	-28.8	10.9	-2.63	3434	.008

	Estimate	SE	tStat	DF	pValue
(Intercept)	339	31.3	10.8	3424	<.001
TrialIndex	-29	15.2	-1.91	3424	.056
Group_Patient	-37.4	51.3	-0.729	3424	.466
Manuality_Bimanual	-6.35	8.48	-0.749	3424	.454
PressingHand_NonDom	11.5	4.25	2.71	3424	.007
Feedback_Blindfolded	-3.45	4.29	-0.806	3424	.420
StraightLineDistance	1.08	0.0322	33.5	3424	<.001
TrialIndex: Group_Patient	96.5	25.9	3.72	3424	<.001
Group_Patient: Manuality_Bimanual	-56	36	-1.55	3424	.120
Group_Patient: PressingHand_NonDom	-73.3	31.8	-2.3	3424	.021
Group_Patient: Feedback_Blindfolded	-14.6	20.8	-0.7	3424	.484
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	-28.6	10.9	-2.64	3424	.008

4.3.3 Maximum speed

Summary statistics are presented in Figure 21. Estimates from the regression model are presented in Table 9. The maximum speed was positively correlated with the straight-line distance. Under the reference condition, the difference between the two groups was not a significant predictor of maximum speed, nor was the effect of blindfolding or trial index. When pressing with the non-dominant hand, the comparison group were estimated to be significantly faster than when pressing with the dominant hand, but the difference was small. In contrast, the significant difference between the patient group's paretic and non-paretic hands was large. Manuality was not a significant predictor of maximum speed for the comparison group under the reference condition. This was also true for the patient group, whether they were pressing with the paretic or non-paretic hand.

Excluding sequential reaches did not affect these conclusions. 21 trials (0.61%) were identified as outliers. This included 18 comparison group trials (0.78%) and 3 patient group trials (0.26%). The conclusions were the same when the model was refitted with these trials excluded (Table 9).

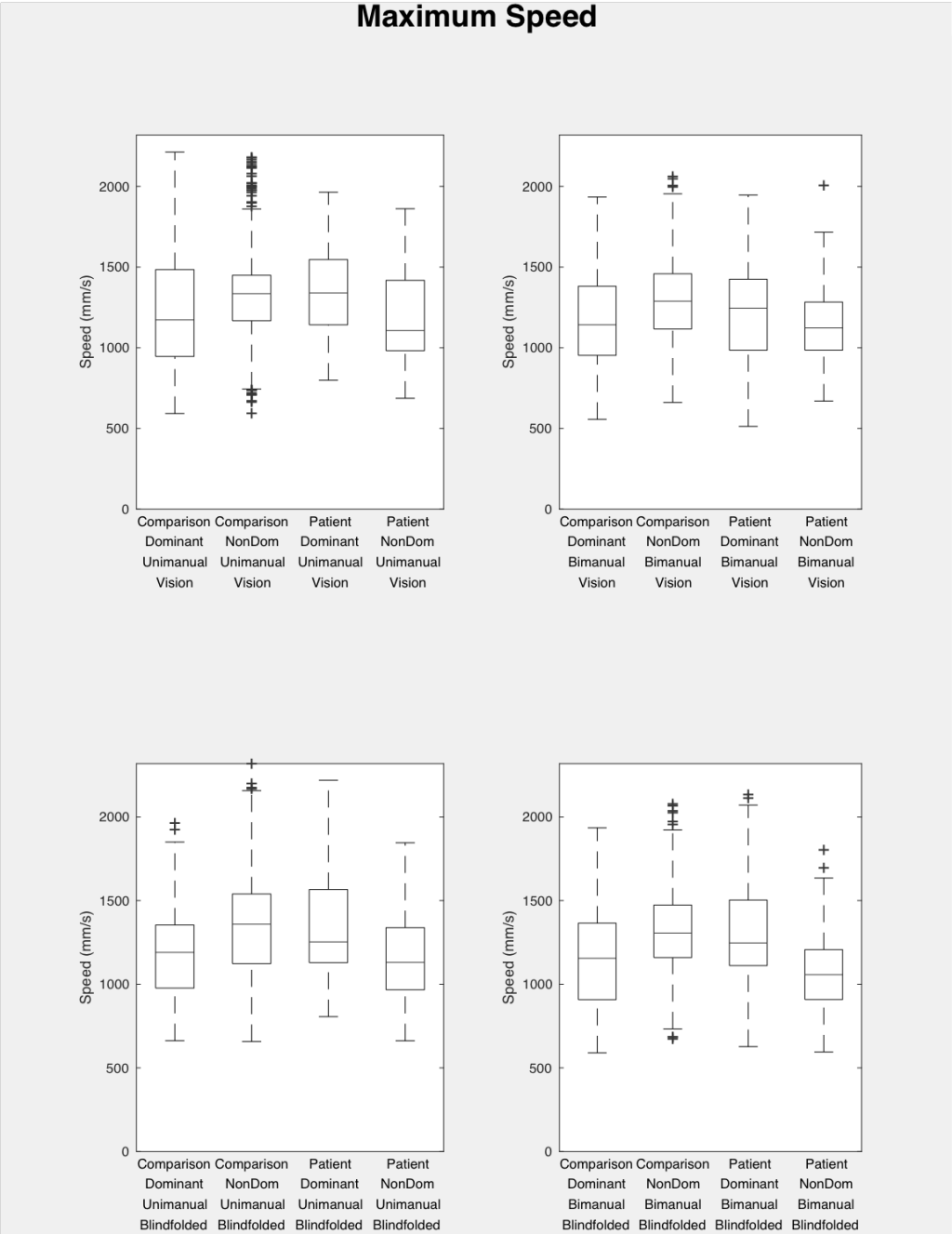

Figure 21. Maximum speed box-plots

On each box, central mark is median, edges of box are 25th and 75th percentiles, whiskers extend to most extreme datapoints algorithm considers to be not outliers, and outliers are plotted individually. Points are outliers if they larger than Q3+1.5(Q3-Q1) or smaller than Q1-1.5*(Q3-Q1), where Q1 and Q3 are the 25th and 75th percentiles, respectively.*

Table 9. Maximum speed regression estimates

Top, estimates with outliers included. Bottom, estimates with outliers excluded. For definition of an outlier see Statistical Analysis section. Estimate = estimated coefficient; SE = standard error of coefficient; tStat = t-statistic; DF = degrees of freedom for t-test; pValue = p-value for t-test

	Estimate	SE	tStat	DF	pValue
(Intercept)	493	53.8	9.15	3434	<.001
TrialIndex	-31.1	26.4	-1.18	3434	.239
Group_Patient	34	88.1	0.386	3434	.700
Manuality_Bimanual	-22.4	14.8	-1.51	3434	.130
PressingHand_NonDom	29.5	7.4	3.98	3434	<.001
Feedback_Blindfolded	-10.3	7.48	-1.37	3434	.170
StraightLineDistance	2.22	0.0562	39.5	3434	<.001
TrialIndex: Group_Patient	122	45.3	2.7	3434	.007
Group_Patient: Manuality_Bimanual	-81.5	59.7	-1.37	3434	.172
Group_Patient: PressingHand_NonDom	-301	76.8	-3.91	3434	<.001
Group_Patient: Feedback_Blindfolded	-10.4	35.6	-0.293	3434	.770
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	-21.6	19	-1.14	3434	.255

	Estimate	SE	tStat	DF	pValue
(Intercept)	501	53.4	9.37	3413	<.001
TrialIndex	-23.7	26.3	-0.901	3413	.367
Group_Patient	38.8	87.4	0.444	3413	.657
Manuality_Bimanual	-22.3	14.7	-1.51	3413	.130
PressingHand_NonDom	28.2	7.36	3.83	3413	<.001
Feedback_Blindfolded	-10.4	7.44	-1.4	3413	.162
StraightLineDistance	2.19	0.0561	39	3413	<.001
TrialIndex: Group_Patient	114	45	2.54	3413	.011
Group_Patient: Manuality_Bimanual	-83.5	59.4	-1.41	3413	.160
Group_Patient: PressingHand_NonDom	-296	74.9	-3.95	3413	<.001
Group_Patient: Feedback_Blindfolded	-12.9	33.2	-0.389	3413	.698
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	-19.2	18.8	-1.02	3413	.307

4.3.4 Length index

Summary statistics are presented in Figure 22. Estimates from the regression model are presented in Table 10. Under the reference condition, the difference in length index between the two groups was not significant, nor was the effect of blindfolding (Table 10, Figure 22). Length index was significantly negatively correlated with trial number though. The effect on the patient group was not significantly different. The length index of the comparison group when pressing with the non-dominant hand was slightly lower than the dominant under the reference condition. In contrast, the length index was substantially higher for the patient group when pressing with the paretic hand. The length index during bimanual trials was significantly greater for the comparison group. The difference in length index between bimanual and unimanual trials was estimated to be much smaller for the patient group, but there was a lot of variability in this measure, hence the group difference was not significant.

103 trials (2.99%) were identified as outliers. This included 32 comparison group trials (1.39%) and 71 patient group trials (6.21%). When outliers were excluded from the analysis, the interaction between group and manuality was significant and the length index of the patient group during bimanual trials was estimated to be only slightly greater than during unimanual trials (Table 10). This effect could have been driven by sequential reaching, since sequential reaches are essentially sequential unimanual reaches. However, when both outliers and sequential reaches were excluded from the analysis, there was still a trend (p = .10) toward a large group difference, with patients having only a slightly higher length index during bimanual trials.

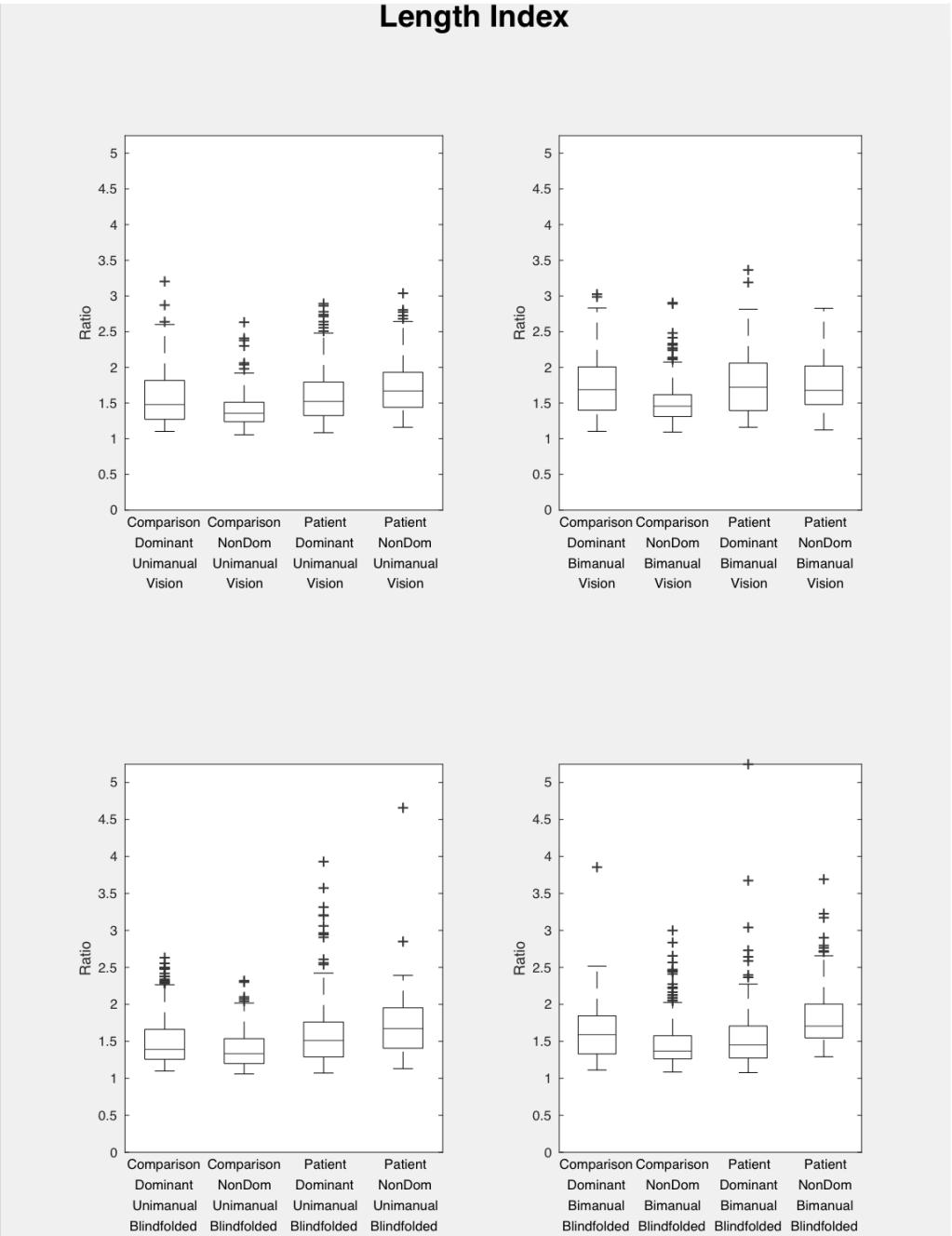

Figure 22. Length index box-plots

On each box, central mark is median, edges of box are 25th and 75th percentiles, whiskers extend to most extreme datapoints algorithm considers to be not outliers, and outliers are plotted individually. Points are outliers if they larger than Q3+1.5(Q3-Q1) or smaller than Q1-1.5*(Q3-Q1), where Q1 and Q3 are the 25th and 75th percentiles, respectively.*

Table 10. Length index regression estimates

Top, estimates with outliers included. Bottom, estimates with outliers excluded. For definition of an outlier see Statistical Analysis section. Estimate = estimated coefficient; SE = standard error of coefficient; tStat = t-statistic; DF = degrees of freedom for t-test; pValue = p-value for t-test

	Estimate	SE	tStat	DF	pValue
(Intercept)	1.6	0.0741	21.6	3435	<.001
TrialIndex	-0.117	0.0481	-2.44	3435	.015
Group_Patient	0.0626	0.129	0.486	3435	.627
Manuality_Bimanual	0.168	0.0269	6.26	3435	<.001
PressingHand_NonDom	-0.166	0.0125	-13.3	3435	<.001
Feedback_Blindfolded	-0.0377	0.0135	-2.78	3435	.005
TrialIndex: Group_Patient	0.0968	0.0822	1.18	3435	.239
Group_Patient: Manuality_Bimanual	-0.109	0.101	-1.08	3435	.282
Group_Patient: PressingHand_NonDom	0.253	0.0665	3.8	3435	<.001
Group_Patient: Feedback_Blindfolded	0.008	0.0414	0.193	3435	.847
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	0.0148	0.0345	0.43	3435	.667

	Estimate	SE	tStat	DF	pValue
(Intercept)	1.58	0.0636	24.9	3332	<.001
TrialIndex	-0.121	0.0393	-3.08	3332	.002
Group_Patient	0.00738	0.111	0.0667	3332	.947
Manuality_Bimanual	0.167	0.022	7.57	3332	<.001
PressingHand_NonDom	-0.152	0.0102	-14.9	3332	<.001
Feedback_Blindfolded	-0.0301	0.0111	-2.72	3332	.007
TrialIndex: Group_Patient	0.161	0.0684	2.35	3332	.019
Group_Patient: Manuality_Bimanual	-0.144	0.072	-2	3332	.045
Group_Patient: PressingHand_NonDom	0.279	0.0601	4.65	3332	<.001
Group_Patient: Feedback_Blindfolded	-0.0219	0.0352	-0.623	3332	.533
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	-0.00656	0.0289	-0.227	3332	.821

4.3.5 Number of movement units

Summary statistics are presented in Figure 23. Estimates from the regression model are presented in Table 11. Straight-line distance was a significant positive predictor of number of movement units. Under the reference condition, group, feedback and trial-index were not significant predictors of number of movement units. When the comparison group pressed with the non-dominant hand under the reference condition, the number of movements was estimated to be significantly less than when pressing with dominant hand though the difference was small. This effect was reversed for the patient group who completed the reach in substantially more movement units when pressing with the paretic hand than when pressing with the non-paretic. Manuality was not a significant predictor of number of movement units for either group.

Excluding sequential reaches did not affect these conclusions. 29 trials (0.84%) were identified as outliers. This included 3 comparison group trials (0.13%) and 26 patient group trials (2.27%). Refitting the model with these outliers removed did not affect any of the above conclusions (Table 11).

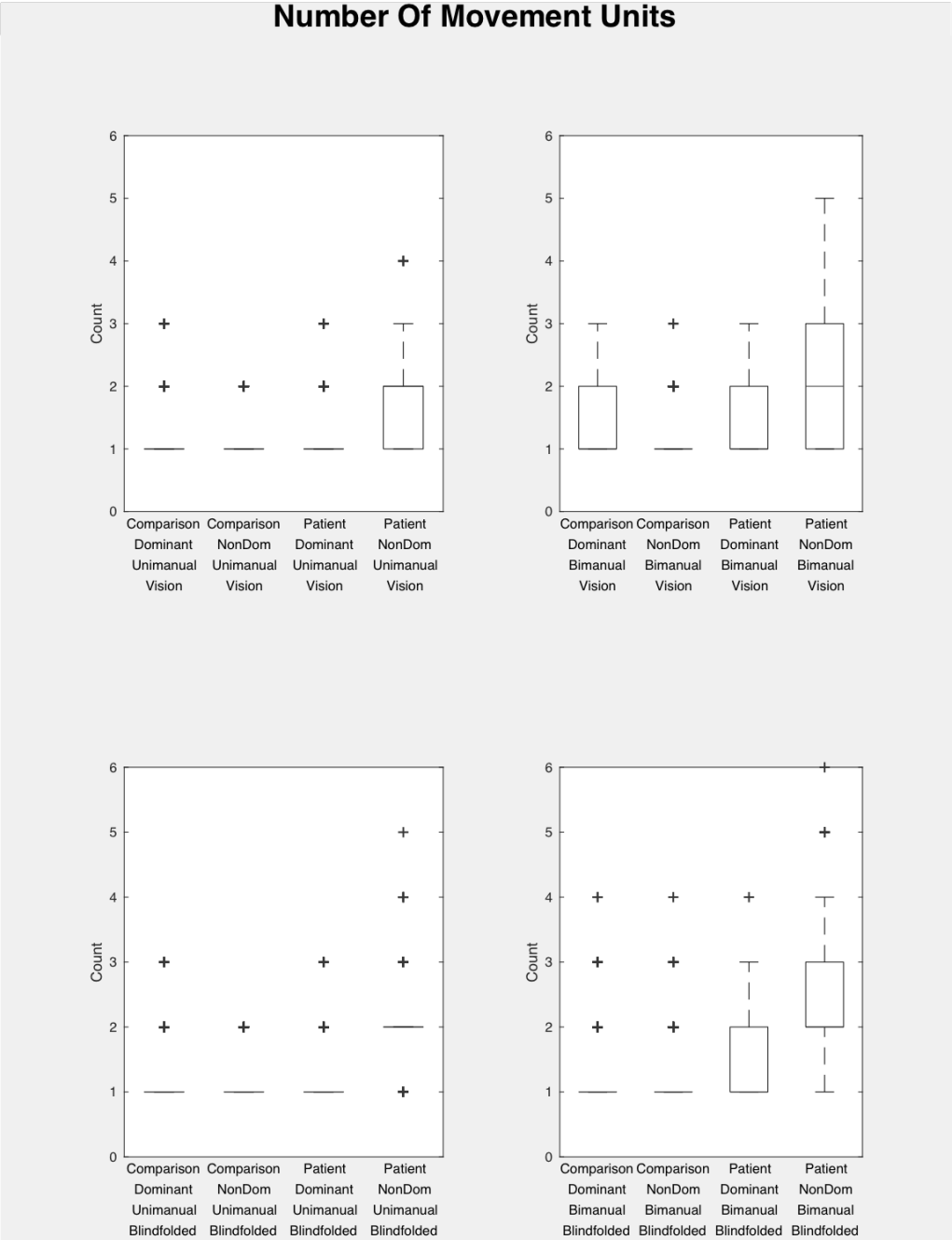

Figure 23. Number of movement units box-plots

On each box, central mark is median, edges of box are 25th and 75th percentiles, whiskers extend to most extreme datapoints algorithm considers to be not outliers, and outliers are plotted individually. Points are outliers if they larger than Q3+1.5(Q3-Q1) or smaller than Q1-1.5*(Q3-Q1), where Q1 and Q3 are the 25th and 75th percentiles, respectively.*

Table 11. Number of movement units regression estimates

Top, estimates with outliers included. Bottom, estimates with outliers excluded. For definition of an outlier see Statistical Analysis section. Estimate = estimated coefficient; SE = standard error of coefficient; tStat = t-statistic; DF = degrees of freedom for t-test; pValue = p-value for t-test

	Estimate	SE	tStat	DF	pValue
(Intercept)	0.0119	0.0842	0.142	3434	.887
TrialIndex	-0.0664	0.151	-0.441	3434	.659
Group_Patient	-0.00073	0.0812	-0.00898	3434	.993
Manuality_Bimanual	0.117	0.0844	1.38	3434	.167
PressingHand_NonDom	-0.116	0.0406	-2.85	3434	.004
Feedback_Blindfolded	-0.00537	0.0425	-0.126	3434	.900
StraightLineDistance	0.000581	0.000219	2.65	3434	.008
TrialIndex: Group_Patient	-0.00837	0.23	-0.0364	3434	.971
Group_Patient: Manuality_Bimanual	0.0709	0.141	0.504	3434	.614
Group_Patient: PressingHand_NonDom	0.487	0.0947	5.14	3434	<.001
Group_Patient: Feedback_Blindfolded	0.0701	0.071	0.987	3434	.324
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	0.00111	0.0928	0.0119	3434	.990

	Estimate	SE	tStat	DF	pValue
(Intercept)	0.0368	0.0839	0.439	3405	.661
TrialIndex	-0.0724	0.151	-0.48	3405	.632
Group_Patient	0.0168	0.0818	0.205	3405	.838
Manuality_Bimanual	0.114	0.0845	1.35	3405	.178
PressingHand_NonDom	-0.111	0.0407	-2.72	3405	.007
Feedback_Blindfolded	-0.00985	0.0426	-0.231	3405	.817
StraightLineDistance	0.000513	0.000218	2.36	3405	.018
TrialIndex: Group_Patient	-0.0286	0.233	-0.122	3405	.903
Group_Patient: Manuality_Bimanual	0.0798	0.142	0.562	3405	.574
Group_Patient: PressingHand_NonDom	0.456	0.0876	5.2	3405	<.001
Group_Patient: Feedback_Blindfolded	0.0521	0.0705	0.738	3405	.460
Group_Patient: Manuality_Bimanual: PressingHand_NonDom	-0.0196	0.0947	-0.207	3405	.836

4.3.6 Bimanual lag

Summary statistics are presented in Figure 24. Estimates from the regression model are presented in Table 12 and Table 13. Greater straight-line distances were associated with significantly greater end lag. Onset and end lag were not significantly different if participants pressed with the dominant or non-dominant hand. For the comparison group, onset and end lag did not change significantly over the course of a session, but for the patient group onset (but not end) lag substantially decreased. Blindfolding the comparison group did not have a significant effect on onset lag, but end lag increased. Blindfolding the patient group was associated with a greater increase in onset lag. The effect was not significant for end lag.

To test if the results were biased by outliers, the model was refitted with outliers excluded (Table 12 and Table 13). For onset lag, 164 trials (9.53%) were identified as outliers. This included 5 comparison group trials (0.43%) and 159 patient group trials (27.90%). With these trials excluded blindfolding led to a significant but small increase in the onset lag of the comparison group. For end lag, 110 trials (6.40%) were identified as outliers. This included 5 comparison group trials (0.44%) and 105 patient group trials (18.42%). When these trials were removed from the model of end lag, the interaction between group and feedback was also associated with a significant increase in end lag.

When sequential reaches were removed from the end lag model the main effect of group was no longer significant, suggesting it was driven by sequential reaches. Excluding sequential reaches did not change any of the conclusions regarding onset lag.

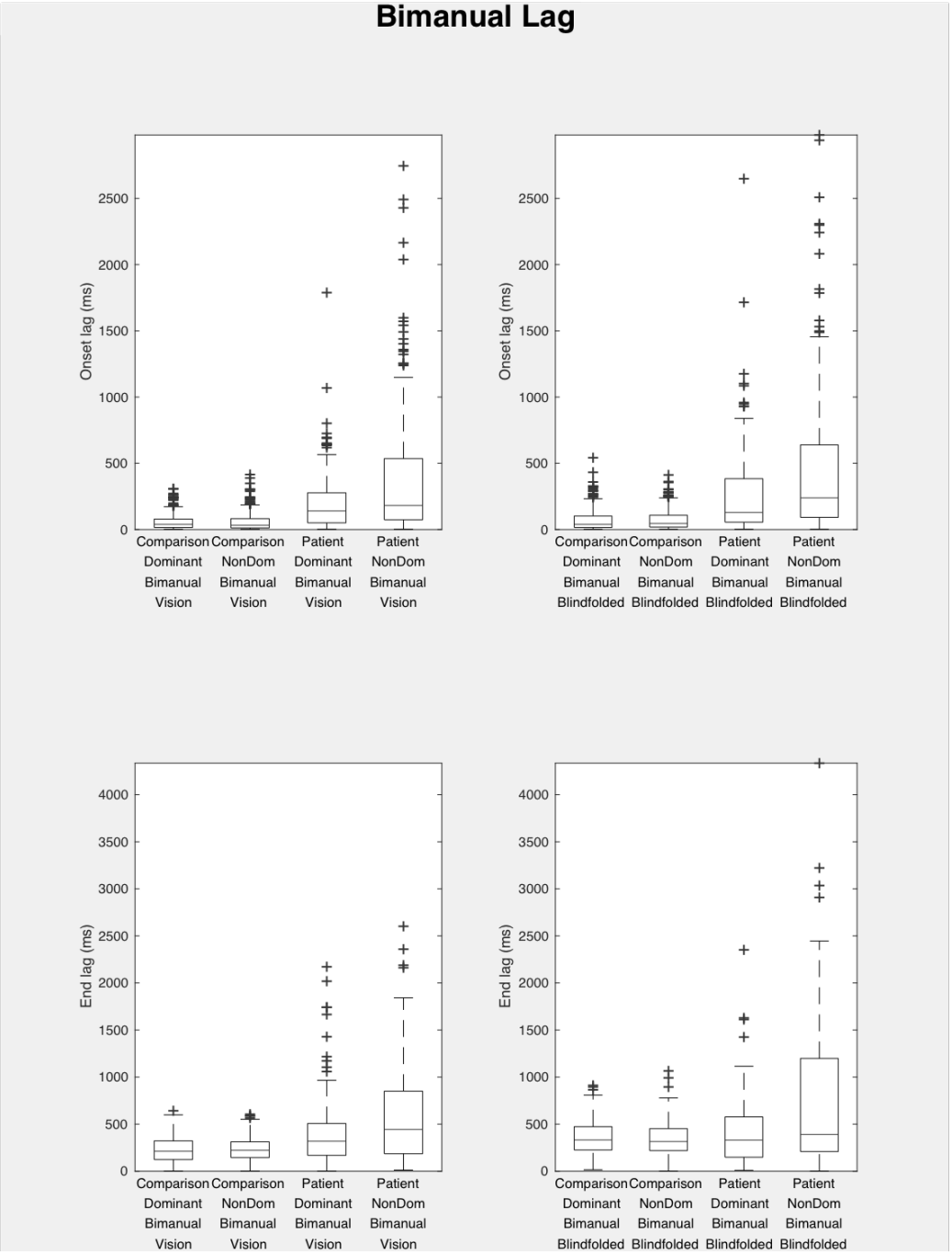

Figure 24. Onset and end lag box-plots

On each box, central mark is median, edges of box are 25th and 75th percentiles, whiskers extend to most extreme datapoints algorithm considers to be not outliers, and outliers are plotted individually. Points are outliers if they larger than Q3+1.5(Q3-Q1) or smaller than Q1-1.5*(Q3-Q1), where Q1 and Q3 are the 25th and 75th percentiles, respectively.*

Table 12. Onset lag regression estimates

Top, estimates with outliers included. Bottom, estimates with outliers excluded. For definition of an outlier see Statistical Analysis section. Estimate = estimated coefficient; SE = standard error of coefficient; tStat = t-statistic; DF = degrees of freedom for t-test; pValue = p-value for t-test

	Estimate	SE	tStat	DF	pValue
(Intercept)	97.3	52.3	1.86	1712	.063
TrialIndex	10.6	47.1	0.224	1712	.823
Group_Patient	352	73.5	4.79	1712	<.001
PressingHand_NonDom	6.95	13.1	0.531	1712	.596
Feedback_Blindfolded	13.6	13.3	1.02	1712	.309
StraightLineDistance	-0.138	0.0959	-1.44	1712	.149
TrialIndex: Group_Patient	-287	78.7	-3.65	1712	<.001
Group_Patient: PressingHand_NonDom	222	129	1.72	1712	.086
Group_Patient: Feedback_Blindfolded	98.9	38	2.6	1712	.009

	Estimate	SE	tStat	DF	pValue
(Intercept)	42	20.2	2.08	1547	.038
TrialIndex	13.6	16.1	0.846	1547	.398
Group_Patient	140	31.6	4.44	1547	<.001
PressingHand_NonDom	-1.47	4.5	-0.327	1547	.744
Feedback_Blindfolded	10.5	4.55	2.31	1547	.021
StraightLineDistance	0.0244	0.0347	0.702	1547	.483
TrialIndex: Group_Patient	-101	30.8	-3.27	1547	.001
Group_Patient: PressingHand_NonDom	19.9	23.2	0.859	1547	.390
Group_Patient: Feedback_Blindfolded	4.05	15.5	0.261	1547	.794

Table 13. End lag regression estimates

Top, estimates with outliers included. Bottom, estimates with outliers excluded. For definition of an outlier see Statistical Analysis section. Estimate = estimated coefficient; SE = standard error of coefficient; tStat = t-statistic; DF = degrees of freedom for t-test; pValue = p-value for t-test

	Estimate	SE	tStat	DF	pValue
(Intercept)	437	62.6	6.98	1712	<.001
TrialIndex	-75.2	59.9	-1.26	1712	.210
Group_Patient	159	85.6	1.86	1712	.063
PressingHand_NonDom	20.9	16.6	1.25	1712	.210
Feedback_Blindfolded	134	17	7.9	1712	<.001
StraightLineDistance	-0.471	0.12	-3.92	1712	<.001
TrialIndex: Group_Patient	-8.4	100	-0.0838	1712	.933
Group_Patient: PressingHand_NonDom	268	186	1.44	1712	.151
Group_Patient: Feedback_Blindfolded	-53.8	72.2	-0.746	1712	.456

	Estimate	SE	tStat	DF	pValue
(Intercept)	367	41.7	8.81	1601	<.001
TrialIndex	-69	36.3	-1.9	1601	.057
Group_Patient	101	61.2	1.65	1601	.099
PressingHand_NonDom	9.01	10.1	0.888	1601	.375
Feedback_Blindfolded	126	10.3	12.3	1601	<.001
StraightLineDistance	-0.264	0.077	-3.43	1601	<.001
TrialIndex: Group_Patient	-6.89	66.2	-0.104	1601	.917
Group_Patient: PressingHand_NonDom	48.3	43.8	1.1	1601	.271
Group_Patient: Feedback_Blindfolded	-110	39	-2.81	1601	.005

4.3.7 Sequential reaches

The comparison group did not perform any sequential reaches (Table 14). From the patient group, C.B. and E.B. did not perform any sequential reaches, D.N. and J.S. performed a small number, but H.W. and P.O performed many sequential reaches (Table 15). These occurred most often when the paretic hand was the pressing hand. Bimanual movement time was high for all participants except for H.W. and P.O. (Figure 25).

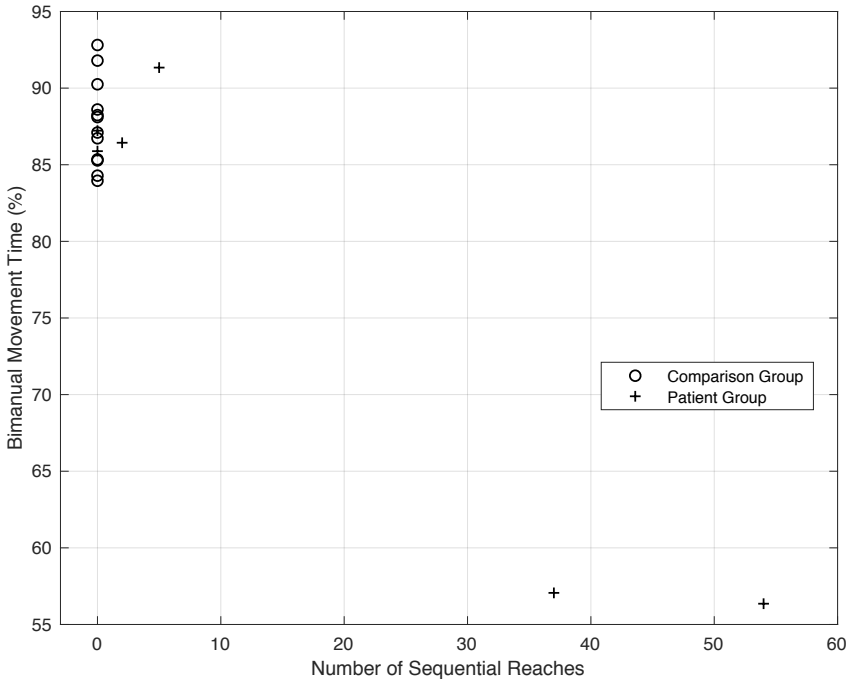

Figure 25. Number of sequential reaches and bimanual movement time

The number of sequential movements was defined as the number of bimanual trials for which reach end of either arm preceded reach onset of the other arm. Bimanual movement time was defined as the percent of the reach phase where the speed of both arms was above 5 cm/s was calculated. The two members of the patient group with the lowest bimanual movement time and highest number of sequential reaches were P.O. (who had the highest number of sequential reaches) and H.W.

Table 14. Sequential reaches, group values

Group	Pressing Hand	Feedback	Percent of trials
Comparison	Dominant	Vision	0
Comparison	Dominant	Blindfolded	0
Comparison	Non-dominant	Vision	0
Comparison	Non-dominant	Blindfolded	0
Patient	Dominant	Vision	6
Patient	Dominant	Blindfolded	16
Patient	Non-dominant	Vision	23
Patient	Non-dominant	Blindfolded	24

Table 15. Sequential reaches, patient values

Patient	Pressing Hand	Feedback	Percent of trials
CB	Dominant	Vision	0
CB	Dominant	Blindfolded	0
CB	NonDominant	Vision	0
CB	NonDominant	Blindfolded	0
DN	Dominant	Vision	0
DN	Dominant	Blindfolded	0
DN	NonDominant	Vision	4
DN	NonDominant	Blindfolded	4
EB	Dominant	Vision	0
EB	Dominant	Blindfolded	0
EB	NonDominant	Vision	0
EB	NonDominant	Blindfolded	0
HW	Dominant	Vision	13
HW	Dominant	Blindfolded	38
HW	NonDominant	Vision	46
HW	NonDominant	Blindfolded	61
JS	Dominant	Vision	0
JS	Dominant	Blindfolded	0
JS	NonDominant	Vision	4
JS	NonDominant	Blindfolded	17
PO	Dominant	Vision	25
PO	Dominant	Blindfolded	54
PO	NonDominant	Vision	83
PO	NonDominant	Blindfolded	65

4.3.8 Individual estimates for patients

Estimates for individual patients were often significantly different from those estimated for the patient group (Table 16). C.B.'s performance with her paretic arm was closer to the performance of her non-paretic than the values estimated for the patient group (i.e. compared to the fixed effect interaction group:pressing-hand): she had significantly shorter movement time, higher average speed and higher maximum speed. Whilst J.S. had shorter movement times with his paretic arm, he also had lower maximum speed. Based on the same comparison, both E.B. and H.W. had lower average speed with their paretic arm. E.B. also had lower maximum speed and H.W. had longer movement times and greater length index. Relative to the patient group estimate, P.O. had substantially greater bimanual onset and end lag when pressing the dispenser with his paretic arm, compared to when pressing with his non-paretic.

E.B.'s performance during bimanual trials compared to unimanual trials was significantly worse than the patient group estimate (i.e. compared to the fixed effect interaction group:manuality): she had longer movement time and lower average and maximum speed than the group estimate. In contrast, J.S. performed better than the group estimate, with shorter movement times and faster average speed. For C.B., the estimated difference between bimanual and unimanual reaching on length index was lower than the group estimate, whilst for D.N. it was significantly greater.

Blindfolding had less of an effect on the reaching performance of J.S. than the group estimate (i.e. compared to the fixed effect interaction group:pressing-hand): movement times were lower and average and maximum speeds were higher. In contrast, D.N. had significantly greater length index when blindfolded and E.B. lower average speed, compared to the group estimate. Blindfolding had less of an effect on the bimanual end lag of D.N. but a greater effect on P.O. and H.W., who also had a greater onset lag than the group estimate.

Table 16. Significant random effects

Only those random effects estimated for patients with p-values < .05 are included here. Estimate = Best linear unbiased predictor (BLUP) of random effect; SEPred = Standard error of the estimate (BLUP minus random effect); tStat = t-statistic for a test that the random effect is zero; DF = Estimated degrees of freedom for the t-statistic; pValue = p-value for t-statistic

	Factor	Patient	Estimate	SEPred	tStat	DF	pValue
MovementTime	Group_Patient:PressingHand_NonDom	C.B.	-69.9	33	-2.12	3434	.034
AverageSpeed	Group_Patient:PressingHand_NonDom	C.B.	153	33.3	4.6	3434	<.001
MaximumSpeed	Group_Patient:PressingHand_NonDom	C.B.	278	78.4	3.55	3434	<.001
LengthIndex	Group_Patient:Manuality_Bimanual	C.B.	-0.402	0.0961	-4.18	3435	<.001
OnsetLag	Group_Patient:PressingHand_NonDom	C.B.	-347	133	-2.61	1711	.009
EndLag	Group_Patient:PressingHand_NonDom	C.B.	-573	191	-3	1711	.003
LengthIndex	Group_Patient:Feedback_Blindfolded	D.N.	0.152	0.0485	3.14	3435	.002
LengthIndex	Group_Patient:Manuality_Bimanual	D.N.	0.274	0.096	2.85	3435	.004
EndLag	Group_Patient:Feedback_Blindfolded	D.N.	-188	79.8	-2.35	1711	.019
MovementTime	Group_Patient:Manuality_Bimanual	E.B.	140	31.2	4.48	3434	<.001
AverageSpeed	Group_Patient:PressingHand_NonDom	E.B.	-65.3	33.2	-1.96	3434	.050
AverageSpeed	Group_Patient:Feedback_Blindfolded	E.B.	-46.1	22.8	-2.02	3434	.043
AverageSpeed	Group_Patient:Manuality_Bimanual	E.B.	-155	34.6	-4.48	3434	<.001
MaximumSpeed	Group_Patient:PressingHand_NonDom	E.B.	-162	78.3	-2.07	3434	.038
MaximumSpeed	Group_Patient:Manuality_Bimanual	E.B.	-268	57.1	-4.7	3434	<.001
MovementTime	Group_Patient:PressingHand_NonDom	H.W.	107	32.8	3.26	3434	.001
AverageSpeed	Group_Patient:PressingHand_NonDom	H.W.	-65.2	33.2	-1.97	3434	.049
LengthIndex	Group_Patient:PressingHand_NonDom	H.W.	0.249	0.071	3.5	3435	<.001
OnsetLag	Group_Patient:Feedback_Blindfolded	H.W.	130	44.6	2.93	1711	.003
EndLag	Group_Patient:Feedback_Blindfolded	H.W.	200	80	2.5	1711	.012
MovementTime	Group_Patient:PressingHand_NonDom	J.S.	-82.5	32.8	-2.51	3434	.012
MovementTime	Group_Patient:Feedback_Blindfolded	J.S.	-89.6	22.4	-3.99	3434	<.001
MovementTime	Group_Patient:Manuality_Bimanual	J.S.	-69.3	31.2	-2.22	3434	.026
AverageSpeed	Group_Patient:Feedback_Blindfolded	J.S.	98	22.8	4.3	3434	<.001
AverageSpeed	Group_Patient:Manuality_Bimanual	J.S.	73.4	34.6	2.12	3434	.034
MaximumSpeed	Group_Patient:PressingHand_NonDom	J.S.	-277	78.2	-3.54	3434	<.001
MaximumSpeed	Group_Patient:Feedback_Blindfolded	J.S.	168	38.9	4.31	3434	<.001
LengthIndex	Group_Patient:PressingHand_NonDom	P.O.	-0.226	0.0711	-3.18	3435	.001
OnsetLag	Group_Patient:PressingHand_NonDom	P.O.	624	133	4.7	1711	<.001
EndLag	Group_Patient:PressingHand_NonDom	P.O.	887	190	4.66	1711	<.001
EndLag	Group_Patient:Feedback_Blindfolded	P.O.	219	79.9	2.74	1711	.006

4.4 Discussion

4.4.1 Unimanual motor performance

The current study provides the first group analysis of upper limb kinematics after hemispherectomy. Previous studies of patients with unilateral cerebral palsy who had not undergone hemispherectomy found reach impairments in terms of movement time, speed, curvature and number of movement units (Domellöf et al. 2009; Steenbergen et al. 2000a; Steenbergen et al. 2000b). Similarly, for the hemispherectomy group, movement times of the paretic arm were estimated to be higher, average speed was lower, maximum speed was lower, length index was higher and the number of movement units higher, compared to the non-paretic arm. Reaching with the paretic arm was, therefore, slower, more fractionated and less direct. In contrast, when reaching with non-dominant arm the comparison group performed significantly better than with the dominant, although the differences were far smaller than between the paretic and non-paretic arms of the patient group. Given the size of the differences for the patient group, it would be of interest to compare the results to a group of patients with unilateral cerebral palsy who had not undergone hemispherectomy, to see if the groups are similar in the extent of their impairments.

Contrary to expectations, when considering the non-paretic arm, the patient group's movements were not statistically significantly different to the comparison group by any performance measure. Given the results of previous studies, this was surprising. It has previously been shown that hemispherectomised patients have reduced strength and tapping speed of the non-paretic arm relative to a comparison group (Dijkerman et al. 2008). Similar deficits have been found in patients with unilateral cerebral palsy (Dellatolas et al. 2005) and those with unilateral adult-acquired stroke (Colebatch and Gandevia 1989; Prigatano and Wong 1997), suggesting non-paretic arm impairments could be common to all hemiparetic cohorts. In addition to these findings, when reaching with the non-paretic arm, adult-stroke patients have been found to have longer reach duration, lower mean

speed and a greater number of movement units, irrespective of the side of the lesion (Hermsdorfer et al. 1999a; Schaefer et al. 2007; Yarosh et al. 2004) and patients with unilateral cerebral palsy have been shown to have longer reach duration (Steenbergen and Meulenbroek 2006).

To understand why these differences weren't replicated in this cohort it is important to consider the differences between the task carried out here and in other kinematic studies. Other studies have concurrently scored participants in terms of accuracy (Schaefer et al. 2007; Yarosh et al. 2004). This may have drawn out differences that were more related to the ability to plan and execute an accurate action than the simple reach and press task of the current study. Furthermore, other studies have tested wrist rotation (Yarosh et al. 2004) or fine motor control (Hermsdorfer et al. 1999a), whilst the current study was assessing a broadly gross motor action. Dijkerman et al. (2008) found deficits in the non-paretic arm of hemispherectomised patients. One important distinction with the cohort of the current study, though, is that patients were selected only if they could perform goal-directed reaching. This meant that patients without gross motor function were excluded from the study and, considering that Dellatolas (2005) found non-paretic arm deficits in only 30% of hemiparetic children, the difference in result could be due to the sampling procedure. To test this one could repeat the current assessment of this arm, but apply it to hemispherectomised patients with a range of abilities.

4.4.2 Inter-limb synchronisation

When healthy participants perform bimanual reaching, there is a tendency to synchronise the arms in terms of the times of movement onset and end (Kelso et al. 1979), even when the action is asymmetric (Fowler et al. 1991; Kazennikov et al. 2002; Kazennikov et al. 1994; Marteniuk et al. 1984; Perrig et al. 1999). Hung and colleagues (Hung et al. 2004; 2010) found that bimanual synchronisation during asymmetric action is not as strong for patients with cerebral palsy: the duration over which the two arms move in tandem is significantly lower than healthy participants and the latencies at

movement onset and end are greater. In the current study, this effect was found to be particularly large for hemispherectomised patients and, on many occasions, patients moved the arms sequentially, waiting for one arm to finish the action before setting the next arm in motion.

This effect was present for every patient, though the difference was especially great for H.W. and P.O. One interpretation of these results is that motor reorganisation, involving the transfer of motor representations of one limb to the contralateral hemisphere, might have resulted in the left and right arms sharing neural resources. The cortical representations for motor planning and execution of the two limbs may be near or even overlap. This could make it difficult to simultaneously control and execute movements with the left and right arms. Motor reorganisation is more likely to occur during development, when the nervous system is more actively establishing and strengthening neuronal connections (Martin et al. 2007). This might explain why the breakdown in inter-limb synchronisation has been mainly found in patients with cerebral palsy, rather than adult stroke.

The inter-individual differences detected here could provide an opportunity for further investigation. Future research might try to account for this variability by considering differences in the neurological status of the patients. For example, P.O. performs many reaches sequentially – does this indicate that the neural structures that are used for motor control of the non-paretic arm overlap with those for the paretic arm? For the other patients, is there less overlap in these structures? Furthermore, onset lag decreased on a trial-by-trial basis. Perhaps with practice hemispherectomised patients may be able to overcome this impairment. Future studies could investigate both the neural structures involved in motor planning in hemispherectomised patients and the capacity for rehabilitation to address this impairment.

4.4.3 Spatial interference

When healthy participants are asked to perform an asymmetric action, the movement of one arm may disturb the intended trajectory of the other. This has been demonstrated for rather artificial actions, such as concurrent line

and circle drawing, which have been designed for experimental testing in the laboratory (Carson et al. 1997; Semjen et al. 1995). In the current study, it has been shown that for a simple, self- paced, everyday reaching task, concurrent use of one arm changes the trajectory of the other arm, i.e. bimanual reaching was associated with a greater length index than unimanual reaching. These results suggest that spatial interference is a feature, not only of artificial tasks designed for the laboratory, but persists in everyday functional actions. As with inter-limb synchronisation, this might represent the tendency of the central nervous system to control the arms as a single unit. Whilst this may have benefits, by reducing the complexity of the task, it could also result in a less efficient trajectory that deviates further from the most direct path.

Unlike the comparison group, the length index of the patient group during bimanual trials was estimated to be only slightly greater than during unimanual trials. Since some patients often performed reaches sequentially, these reaches could be considered unimanual. However, the group difference was still present when sequential reach trials were excluded from analysis. The effect varied between patients, though. For J.S., E.B and P.O. there was, indeed, approximately no difference between the conditions. For C.B. the difference between bimanual and unimanual reaching, was even lower than the patient group estimate. But for D.N. and H.W. it was higher than the patient group estimate, closer to the comparison group estimate. In other words, compared to the comparison group, levels of inter-limb spatial interference may be lower for hemispherectomised patients in general, but the effect is different for different patients.

In healthy participants, spatial interference is believed to occur due to the inter-hemispheric transfer of motor plans for the left and right limbs via the corpus callosum (Franz et al. 1996a), perhaps due to a bilateral network containing the dorsolateral prefrontal cortex, anterior cingulate, and supramarginal gyrus (Wenderoth et al. 2005). In the hemispherectomised patient who has retained function of the paretic limb, the brain must have reorganised to allow bimanual function. It is unknown how motor commands

for the two arms can be represented in a single cerebral hemisphere, though, and how or whether these commands are exchanged and integrated. The results here suggest that, for some hemispherectomised patients, integration of spatial commands for the left and right arms may be lower than for healthy individuals. Future studies might attempt to differentiate between the performance of hemispherectomised patients with a more traditional bimanual interference task, such as simultaneous line and circle drawing, and then ask how the representations for the left and right arms are represented in the cortex. It might also be possible to explain inter-individual differences in terms of measures of anatomical connectivity between these structures.

4.4.4 Vision

If the execution of an action is dependent on visual feedback one would expect that removal of visual feedback would affect the kinematics of the action. For the task studied here, the participants may have used visual feedback of their hands and the dispenser to complete the reach. If so, one would expect blindfolding the comparison group to have a significant effect on their kinematics. The effect was estimated to be small and non-significant in terms of movement time, average speed, maximum speed and number of movement units. This suggests that the comparison group were not utilising visual feedback to modify these kinematic variables.

This confirms the results of other studies. When Jakobson and Goodale (1991) and Carella et al. (2003) removed vision they found no change in the kinematic variables including movement time. Similarly, when Wing, Turton and Fraser (1986) blindfolded subjects, movement times were comparable. There have been contradictory results though. When subjects were blindfolded, Chieffi and Gentilucci (1993) found subjects were slower and had longer movement times, whilst Jeannerod (1984) found that subjects took longer when visual feedback was available. The only significant effect of blindfolding was a decrease in length index indicating a more direct reach trajectory. This was surprising, but one might speculate that without vision

participants were more conservative with their trajectories. Again, results from other studies are contradictory: Sergio and Scott (1998) found the curvature of healthy participants to be higher when blindfolded, whilst Carella et al. (2003) found that the length index was not significantly different. The lack of consistency across studies could indicate that the use of visual feedback is highly dependent on the task being studied. To confirm this one could investigate the reliability of these effects by attempting to replicate the previous studies.

In Chapter 3 it was demonstrated that the patients studied here have profound visual deficits. When visual feedback was available, this could have led to performance differences between the groups if the comparison group were utilising visual feedback to modify the kinematic variables of reaching. Since this does not seem to have been the case, one would instead predict that the effect of blindfolding would be similar for both groups. The results confirm this: the effect of removing visual feedback on the comparison group's kinematics was not significantly different to the effect on the patient group, whether outliers and/or sequential bimanual reach trials were excluded from the analysis or not. This further supports the hypothesis that dependence on visual feedback for the reaching task was low.

4.4.5 Target distance

It is well established that, for healthy participants, average and maximum speed increase with greater target distance (Beggs and Howarth 1972; Fitts 1954; Wadman et al. 1979). These results were replicated here. For naturally paced actions Jeannerod (1984) claimed that, despite increases in distance, movement times are mostly invariant, i.e. speed is scaled in line with the distance travelled. In the current study, despite being a self-paced action, speed was not fully scaled to compensate for the increased total distance – movement times showed an increase with greater distance. Whilst Jeannerod reported movement time as invariant across different distances, he only tested this in three participants, who performed only six reaches each. Due to variation between-subjects, he calculated correlation

coefficients individually. Although two participants had low coefficients with high p-values, for one of the participants the coefficient was high and p-value significant ($r = .76$, $p < .01$). In the current study, many trials were analysed in a linear mixed effects model, accounting for a repeated measures design and inter-individual differences. A statistically significant but small relationship was found. Jeannerod may not have found a significant correlation for all subjects, then, because the relationship is small and variable, both within and between subjects.

4.4.6 Trial-on-trial differences

A trial index was included in the regression models in case participants improved with practice, had progressively reduced attention or fatigued over the course of the session. For the comparison group, the length index was found to decrease over the course of a session whilst average speed decreased. There was therefore a trial-on-trial change in trajectory, perhaps indicating a learning effect, but also a decrease in speed, which could be caused by fatigue. The effect on the patient group's speed was the opposite: both average and maximum speed increased over the course of a session. Rather than fatiguing then, as might have been expected, the patients moved faster. As the patients practised the task, their confidence may have grown and this may have resulted in an increase in speed. Without further investigation, it is not possible to know why these effects occurred, but the results do show that these measures are sensitive to changes in motor performance over time.

It should be noted that this approach assumed that trial-on-trial changes would be linear. This was not necessarily true: any one of the factors (e.g. fatigue, practice or attention) may have affected performance in a non-linear pattern, or there may have been interactions between different factors that caused a non-linear effect on the dependent variable. Future studies may wish to investigate this with non-linear modelling approaches, or by measuring individual factors. For example, at the end of a block participants

could be asked to provide a self-report of levels of fatigue and ability to concentrate on the task.

4.4.7 Inter-individual differences

The results discussed so far relate to group differences, but it is important to consider performance differences between patients, too. For example, the patients varied significantly in terms of the speed of their paretic arm compared to the non-paretic, after controlling for the differences between the comparison group's dominant and non-dominant arms: the average and maximum speed of C.B. was higher than the group estimate, whilst the maximum speed of J.S. and the average speed of E.B. and H.W. were below the group estimate. H.W. had higher length index indicating a less direct movement. By incorporating motion capture into the motor assessment of patients during rehabilitation, differences between patients such as these could be detected and rehabilitation strategies could be designed and adjusted accordingly.

4.4.8 Limitations

Finally, for the benefit of future work it would be beneficial to consider any difficulties which were encountered in this study. The motor task used here was a new design. The design was successful, but could be improved with some adjustments. Firstly, one goal of the task was to assess the contribution of vision. This was tested by continuously blindfolding participants throughout a block. A disadvantage with this approach was that participants were required to rely on motor and/or kinaesthetic memory of the target location. An alternative approach would be to remove vision shortly before movement onset, at movement onset or mid-flight. This could be achieved by blacking out the room (Day et al. 1998) or using liquid crystal glasses (Day et al. 2010).

Secondly, when processing the data, it became apparent that the task could have been improved by a method for establishing reach onset and end during data capture, rather than estimating these values post-hoc. Reach onset could be determined simply by placing one contact switch on the table

underneath each hand, which issues a trigger when that hand leaves the table. Reach end could be estimated for the pressing hand by similarly placing a contact switch on top of the dispenser. Determining the same value for the other hand (placed beneath the dispenser) would be less simple, since it does not contact any object at reach end. Instead a relatively more sophisticated device could be used, such as an infrared sensor that determines when the hand is near the dispenser.

Thirdly, it is considered best practice for potential difficulties in the analysis of an experiment to be controlled for within the experimental design, rather than solve these difficulties through statistical methods. Here, repeated measures were taken from the same participants under different conditions. This is not ideal, since it violates the standard linear regression assumption of random sampling. It did allow for inter-individual differences to be analysed, though, which were shown to be important. The conditions were not randomised to avoid ordering effects, though. If the order of the conditions did affect the behaviour of the participants then, if the order had been randomised, the effects on the participants would be expected to vary. This would have made analysis of inter-individual differences problematic since the participants would have effectively been tested under difference conditions. The decision was made to not randomise, but instead include the term “trial-index” to account for ordering effects. Previous studies have used this approach to take the effects of trial order under statistical control rather than making those effects less predictable through counter-balancing or randomisation (Baayen et al. 2008). Future studies may wish to investigate alternatives however.

Fractionation of the movement was analysed in terms of distinct movement units. The definition was simple and based on that used by other researchers such as von Hofsten (1991), however it is susceptible to missing subtle changes in the speed profile that might represent multiple submovements. Other highly complex approaches have been developed for detecting subtle submovements (Rohrer and Hogan 2006) which could be investigated in future studies. It should also be noted that a greater number of movement units could be caused by various factors. For example, patients may have

had difficulty sustaining attention through the experiment, difficulty planning an accurate reach to target in a single unit or, being aware of weakness in proximal muscles, chosen to perform it in multiple units that require less sustained muscle contraction of the proximal muscles during each unit.

The analysis of number of movement units involved selecting a valid statistical approach for an ordinal, count variable (generalised linear modelling). The statistical method does not mean that all problems associated with ordinal variables were avoided. For example, the analysis assumes that the difference between two levels is equal, but the difference between performing a reach in one movement unit (perhaps representing pure offline control) and two units (perhaps a feedforward process, plus an online correction) may be more important than the difference between two units and three units (a feedforward process plus two online corrections), but the value difference is still one. An alternative approach would be to analyse the properties of the movement units themselves, at discrete time points within each movement unit (e.g. the midpoint, or at peak speed) and/or over sub-sections of the data (e.g. mean values over the duration of each movement unit).

To account for inter-individual differences, random effects terms were included to estimate (1) individual intercepts for each subject and (2) individual slopes for some of the fixed effects that were of particular interest. A more thorough analysis of these differences might estimate individual slopes for all fixed effects. This would generate a lot of data. For example, 18 different slopes would be estimated for the main effect of feedback. This was deemed unnecessary for testing the a-priori hypotheses of the current study, but might be interesting for further exploratory analysis.

The residuals were not perfectly normally distributed. Whilst regression analysis assumes a normal distribution, the approach is considered to be robust to departures (Seber and Lee 2012). For the present study, the distributions were judged to be close enough to normal to trust the results, although this was a subjective judgement based on visual inspection of the

plots. An alternative approach would have been to use formal tests of normality, heteroscedasticity and autocorrelation, but statisticians consider these approaches to be too strict for these purposes (Field 2013). It should also be noted that, based on the *adjusted* R^2 statistic, the models computed for number of movement units and length index were judged to be poor fits. This indicates that the estimated effects may be inaccurate and should therefore be approached with some caution. The models may have improved given the inclusion of further explanatory variables.

Finally, whilst the bimanual task used proved to be flexible in terms of the conditions it could be performed under, whilst not too demanding so that all patients could perform it, other bimanual tasks could have been considered. The task used was asymmetric reaching that required distinct patterns of muscle activation and different joint rotations with the left and right arms. This may have been particularly difficult to do with one cerebral hemisphere. However, the end-point location of the two hands was similar. For this reason, motor planning in the remaining hemisphere needed to only code the required muscle activations/joint rotations for one range of end-point spatial coordinates. If the end-point locations had been substantially different this may have put a greater demand on the processing of the remaining hemisphere, perhaps leading to greater performance differences. Therefore, it would be interesting to compare task performance to a bimanual task with substantially different end-locations for the two arms.

4.4.9 Summary

This is the first upper limb kinematics study of a group of hemispherectomised patients. It has been shown that the paretic arm is severely impaired by a range of kinematic measures, but the kinematics of the non-paretic arm are not abnormal. The statistical method used not only provides group averages, but also allows for and quantifies individual variation. A significant breakdown in the bimanual synchronisation of hemispherectomised patients has been detected, but it was a deficit that improved with practice. Bimanual spatial interference – usually assessed with

an abstract experimental task – has been measured for a functional task, demonstrating its impact on normal activities. This phenomenon is reduced in hemispherectomised patients, suggesting distinct neural networks for two two limbs, but the effect is different for different patients. This may be the first assessment of spatial interference in hemispherectomised patients. The motor task used here was novel and developed specifically for hemispherectomised patients. It allows for kinematic assessment of both limbs in unimanual and bimanual conditions and does not depend significantly on visual feedback.

5. General discussion

5.1 Introduction

In terms of upper limb movement, clinical evaluation of hemispherectomy candidates has two fundamental goals: (1) to predict the effect of surgery, by determining the extent of ipsilateral control in patients with residual hand function pre-surgery; (2) to assess function and impairment pre- and post-surgery.

The first is currently addressed with fMRI and/or TMS. If prior to surgery: (1) the patient has ipsilateral activity in the sensorimotor cortex during voluntary movement of the contralesional hand, or (2) the contralesional hand muscles respond to TMS of the intact cortex, it is assumed that the remaining hemisphere has some degree of control over the ipsilateral hand muscles. The patient may therefore have a better chance of retaining some hand function after hemispherectomy. Both fMRI and TMS have their disadvantages. fMRI is costly, time-consuming and unsuitable for children who are very young or have severe behavioural problems. Furthermore, the fMRI signal is often too weak to provide conclusive evidence of ipsilateral control. TMS has the potential to elicit a seizure, is not available in all hospitals and may be an intimidating procedure for a child.

The second is currently addressed with clinical outcome measures, such as the Fugl-Meyer Assessment or Action Research Arm Test. These measures are standardised, validated and used widely. The results are quickly recognisable by most clinicians and are useful for comparing patients. They have also drawn on the insights of physiotherapists and other clinicians in the design of the tests. The tests have been designed for other patient types, though. Compared to many other cohorts, even the more able hemispherectomised patients have very poor motor function and severe impairments, yet no motor assessment has been designed specifically for testing them. The use of these measures in previous reports has also led to floor effects (Dijkerman et al. 2008; Holloway et al. 2000). Furthermore, whilst

many clinical outcome measures have good intra and inter operator reliability, they do not provide objective indices of ability.

This thesis has explored two other forms of motor assessment: neurophysiological assessment of motor pathways, and kinematic assessment of unimanual and bimanual reaching.

5.2 Findings from the clinical assessments

5.2.1 Motor function and impairment

In Chapter 2, six patients who had undergone hemispherectomy many years earlier had their motor performance tested with clinical tests of function (Action Research Arm Test) and impairment (Fugl-Meyer Assessment and hand dynamometry). All patients had contralesional upper limb impairments and functional deficits. The extent varied, but ranking of the patients was roughly consistent for the two assessments. Two patients (E.B. and H.W.) had better function than the others and could lift objects with their contralesional hand, such as a small piece of wood, a glass and a marble. Force production with the contralesional hand was low for all patients. J.S. and C.B. were unable to produce any power grip force. The only patient that could produce any key pinch grip force with the contralesional hand was H.W. and output was very low. Patients had greatest difficulty with hand/wrist movement, complex movement combinations and individual joint control. One patient (C.B.) also had impaired ipsilesional fine motor ability.

5.2.2 Vision

Patients are expected to have loss of homonymous hemianopia after hemispherectomy, but all patients also had some loss of the residual hemifield. C.B. and E.B. had extremely poor visual acuity in the contralesional eye and marked or total loss of stereopsis at near. This is in contrast to J.S. who had normal visual acuity, mild deficit of stereopsis at near and minimal loss of vision in his residual hemifield.

5.2.3 MRI

Information regarding the localisation of the lesions was not available in the clinical histories of the patients, however five of the six patients underwent an MRI scan at the time of this study (one patient was excluded due to metal clips). The scans showed complete removal or destruction of the affected hemisphere, with smaller contralesional cerebral peduncles and ipsilesional cerebellar hemispheres for all patients, suggestive of Wallerian degeneration. As such it is highly unlikely that the affected hemisphere provides motor output and, as expected, the patients are likely to be entirely dependent on the remaining hemisphere for any motor control that is sent from the cortex.

5.3 Neurophysiological assessment of motor pathways

5.3.1 Findings

Since Chapter 2 demonstrated that patients retained some functional use of the paretic hand, Chapter 3 asked how this is possible without a functional corticospinal pathway from the affected hemisphere. It was hypothesised that patients with superior upper limb function have shared physiological drive to the left and right upper limb motoneurone pools, indicated by intense persistent mirror movements of the distal upper limb and synchronised muscle activity. This was investigated by firstly testing for mirror movements and then recording muscle activity during attempted bilateral wrist contraction.

Mirror movements were absent for C.B. and J.S., very weak for D.N. and P.O., but for H.W. and E.B they were strong and sustained. For the recording of contralesional wrist muscle activity, C.B., D.N. and J.S. could not sustain a contraction, hence no left-right EMG time and frequency domain analysis was possible. The muscle recordings of the comparison group and P.O. were not correlated in time or frequency domains. For E.B., however, EMG-EMG coherence was identified in low frequency, alpha and high beta frequency ranges. For H.W. coherence maxima were at 10 Hz, 18 Hz, 22 Hz and 42 Hz. The associated cumulant density showed strong left-right muscle activity synchronisation with a large central peak of duration ±10ms. It was

concluded that the patients with relatively better hand function (E.B. and H.W., as demonstrated in Chapter 2) have intense pathological mirror movements and synchronised left and right muscle activity, indicative of bilateral central motor drive to left and right motor units.

5.3.2 Implications for the ipsilateral control of movement

After hemispherectomy the distal upper limb muscle on the paretic side could receive neural drive from a corticospinal pathway or the bilateral ventromedial pathways of the brainstem such as the reticulospinal tract. The results here suggest the pathway for the patients with superior distal upper limb function was corticospinal. In a healthy individual, the major descending motor pathway to the distal upper limb muscles is the crossed corticospinal tract. For this reason it is likely that the non-paretic hand and wrist movements produced by E.B. and H.W. were driven by the corticospinal tract. Since these movements were precisely mirrored by the opposite hand and the signal was precisely synchronised, it is likely that they were controlled by a common pathway. Since the crossed pathway is expected to be corticospinal, it follows that the uncrossed pathway is likely to be corticospinal.

It is possible that a common signal diverges in the cortex, and then follows two distinct descending pathways – one pathway that decussates and travels directly to the spinal cord and another that is relayed via the brainstem. In this case though, one would expect a lag between the signals due to the synaptic delays of the ipsilateral pathway. There was a large central peak in the cumulant density functions with maxima at approximately 0ms. This suggests the motoneurones received synchronous input and hence it seems more likely that both signals travelled directly to the spinal cord – although the value of the lag could not be determined with precision and could have been up to -10 to +10ms. This conclusion is further supported by previous studies though. Studies on mirror movement patients with Klippel-Feil syndrome (Matthews et al. 1990), X-Linked Kallmann Syndrome (Farmer et al. 2004a; Mayston et al. 1997) and congenital hemiplegia (Carr et al. 1993;

Farmer et al. 1991) have also shown motor unit synchronisation shared abnormally between the homologous muscle groups of the left and right limbs. In addition, the following neurophysiological characteristics have been identified that are not shared with typically developing children and adults: (i) strong, short-latency responses to focal TMS, indicative of a fast conducting ipsilateral corticospinal tract; (ii) ipsilateral corticomuscular coherence, indicative of mainly beta rhythm oscillatory drive to ipsilateral spinal motoneurones during voluntary muscle activation; (iii) abnormal crossing of long-latency stretch and cutaneomuscular reflexes with normally organised spinal reflex pathways. Together these findings support the hypothesis that abnormal corticospinal drive occurs in patients with pathological mirror movements.

Although E.B. and H.W. had superior motor function and evidence of common drive, the other patient that could complete the task (P.O.) did not show evidence of common drive. This replicates previous tests of this patient (Vargha-Khadem et al. 1997). In Chapter 2 it was shown that he could perform the same grasp, grip and pinch tasks as E.B. and H.W., but with greater difficulty. In Vargha-Khadem et al.'s study, TMS was applied to the remaining motor cortex, eliciting a contralateral response at 21.5 ms and ipsilateral response at 30 ms. In other studies, when TMS has been used pre-surgery and the latency of the response is the same for left and right sides, hand function has not deteriorated significantly after surgery (Pilato et al. 2009; Rutten et al. 2002; Sun et al. 2009). In contrast, when the latency of the ipsilateral response was greater than the contralateral response, hand function has deteriorated (Sun et al. 2009). The greater latency in ipsilateral responses may be due to synaptic delay along a pathway that relays in the brainstem, e.g. cortico-reticulospinal. Whilst the cortico-reticulospinal tract may have the potential to drive ipsilateral control after brain injury, the size of the pathway to the hand muscles is likely to be small and its involvement may be associated with a range of motor impairments such as spasticity (Riddle et al. 2009).

These results suggest that synchronous bilateral motor unit responses of short latency are indicative of an ipsilateral corticospinal pathway and superior hand function. Where there is a bilateral response with a delay in the ipsilateral motor unit activity, this might represent a strengthened pathway via the brainstem, possibly cortico-reticulospinal. In this case, whilst the patient may have lower functional ability than those with common, bilateral corticospinal drive, the brainstem pathway may still allow for some distal motor control. This issue could be addressed more conclusively by combining the neurophysiological assessment used here with TMS to assess the latency of ipsilateral and contralateral responses in hemispherectomised patients.

5.3.3 Limitations

The capacity of the neurophysiological assessment to predict distal upper limb function is limited by the following factors. Firstly it can only assess certain muscle groups. Since axial muscles receive bilateral corticospinal input in healthy participants one would expect to see a bilateral association (Farmer et al. 1997). The neurophysiological assessment is therefore limited in that it can only predict function after surgery in those muscles that do not receive bilateral input under normal circumstance. However, this limitation is tempered by the likelihood that it is those muscles that do not receive bilateral drive that are most at risk when undergoing hemispherectomy.

The assessment is limited in the range of impairments it could predict. A patient's distal upper limb function is dependent on a range of factors beyond the number of motor units that can be activated by a supraspinal pathway. For example, spasticity can cause significant problems with functional tasks and lead to further problems such as contractures (Lindsay et al. 2015). However an increase or decrease in spasticity is not expected to be predicted by the neurophysiological assessment and so the assessment may not account for a significant effect on distal upper limb function.

The assessment can also only assess patients that have sufficient strength to sustain a steady voluntary contraction. Patients that cannot do this must be

excluded. If used for pre-surgical assessment it is expected that patients that cannot do this pre-surgery are unlikely to be able after surgery, but the motor function of some patients is improved by surgery (Pascoal et al. 2013).

5.3.4 Clinical utility

The clinical utility of a biomarker tool can be assessed by qualitatively considering the benefits and drawbacks of its use compared to established measures. For predicting the effects of hemispherectomy on motor ability, sensorimotor fMRI can be used to identify the areas of the brain that are active during muscle contraction or during sensory stimulation. From this one can determine if movement of or sensation in the paretic hand is associated with activity in the ipsilateral cortex, indicating cortical reorganisation. fMRI is a non-invasive approach and whilst it has inherent risks, such as the effect of the magnetic field on magnetic implants, it is considered safe when used correctly. There are a number of difficulties with this approach though.

Firstly, the cost of an MRI scan is very high (Statista 2015). Compared to other methods there is a low availability of MRI scanners in hospitals in European countries (Eurostat 2017) and the scanner is often in high demand. Since hemispherectomy is a rare procedure it is likely that the hospital where the procedure would take place would have access to the scanner. In developing countries, though, there is much lower availability of MRI scanners (Dechambenoit 2016). Secondly, the procedure requires a high level of cooperation and as such there can be significant difficulties in scanning a child, due to issues such as heightened anxiety and difficulty staying still (Raschle et al. 2012). For this cohort, there is also the possibility that the patient may have a seizure whilst in the scanner. Thirdly, one of the core difficulties with obtaining motor fMRI in this cohort is that the participant must be able to produce a muscle contraction that is strong enough to be detected by fMRI. For weak patients, this may not be possible. An alternative is to use sensory stimulation to determine if there is activation of the ipsilateral sensory areas, though this does not guarantee that the motor areas have also shifted to the ipsilateral side.

TMS can also be used to assess motor reorganisation by measuring the response in the contralesional upper limb to stimulation of the contralesional cortex. TMS is considered a non-invasive approach, although this has been questioned since stimulation has a direct effect on the brain (Davis and van Koningsbruggen 2013). TMS does carry with it certain risks, in particular the possibility of eliciting a seizure, but also potential damage to hearing, local pain, headache, discomfort or cognitive effects (Rossi et al. 2009). The procedure for delivering and recording a single TMS pulse is relatively simple, but it does require the patient (and in the case of a child, their parents/guardians) to agree to what might be an uncomfortable experience. Furthermore, for an accurate recording of the EMG signal the patient must relax their muscles, which children may find difficult.

EMG is a non-invasive tool if surface electrodes are used – as was the case here – and does not carry any significant risks. EMG devices are widely available in hospitals. Although capturing EMG is straightforward, the task used here requires participants to sustain a bilateral contraction with their distal upper limb musculature. An inability to produce any force from the muscles of the paretic hand is not necessarily a problem though, since this is itself an indicator that the patient does not have a functional motor pathway to these muscles. However, some patients may be able to produce some weak output but be unable to sustain this for long enough for EMG to be captured.

In conclusion, fMRI is a high-cost procedure with limited availability that is difficult to administer in the cohort. TMS is not available in many hospitals and has the potential to elicit seizures and other side effects. In contrast, the EMG method used here is low-cost, widely available and non-invasive with little risk to the patient and relatively easy to administer. For these reasons the method is likely to be a useful addition to the pre-operative assessment of hemispherectomised patients.

5.3.5 Future evaluation as a predictive biomarker

Tools that are used to predict the effect of hemispherectomy play a critical role in decision role in making. Given this, a new tool must be thoroughly evaluated before it is accepted. In the following text, a suggested plan for evaluating the validity and reliability of the neurophysiological assessment is proposed.

5.3.6 Analytical validity

Analytical validation is a process to establish that the performance characteristics of a test, tool or instrument are acceptable in terms of its sensitivity, specificity and accuracy. To establish this, one can compare the neurophysiological assessment with the current gold standard for detecting the biomarker. As described under Clinical Utility, a well-established method of demonstrating the existence of a bilateral motor pathway to the distal upper limb musculature is to deliver a single TMS pulse to one hemisphere of the motor cortex whilst recording bilateral EMG from the muscles of interest. A bilateral motor pathway to the distal upper limb musculature is believed to be present if one observes a bilateral motor evoked potential in those muscles. In the case of hemispherectomised patients, one would deliver the TMS pulse to the remaining hemisphere. The tools would then be compared in terms of analytical accuracy, specificity and selectivity (see Table 17) where a positive finding occurs when the tool identifies a bilateral motor pathway to distal upper limb musculature.

5.3.7 Test-retest reliability

Test-retest reliability is defined as the extent to which a measurement is replicated when taken from the same subject under the same conditions. This can be tested by investigating the reliability when taking repeated measurements under the same conditions with the same device (intra-device reliability) and when taking measurements under the same conditions with different devices (inter-device reliability). Repeated measurements can be compared by calculating the intraclass correlation coefficient – a metric that

reflects both the degree of correlation and the agreement between measurements (Koo and Li 2016).

5.3.8 Clinical validity

Clinical validation is a process to establish that a test, tool or instrument acceptably identifies, measures or predicts the concept of interest. To test the clinical validity of the neurophysiological assessment, one can test its performance at predicting distal upper limb function post-hemispherectomy based on pre-surgical testing (see Table 17). A positive clinical outcome could be defined as a score above a pre-specified level on the hand and wrist parts of the Fugl-Meyer Assessment. This level could be defined through discussion with subject matter experts.

5.3.9 Further development

In the future the neurophysiological assessment could be developed to provide further information. Here, only the wrist extensors were investigated. One might improve on this by investigating different distal upper limb muscles: the forearm pronators and supinators and the extrinsic and intrinsic hand muscles. A second issue that could be investigated is the use of needle EMG. The benefit of surface EMG is that it is non-invasive and so more readily accepted by patients. The benefit of needle EMG though, is that one can record direct from the motor unit. For this reason, the noise in the data that is caused by conduction from the motor unit to the surface of the skin is avoided. Furthermore, the variable delays that could be caused by the conduction to the surface of the skin are avoided meaning that the estimate of the lag between the signals is more accurate. These two methods could be compared in terms of test-retest reliability.

Table 17. Definition of tests of validity and reliability

Category	Description
Analytical accuracy	Number of cases where the new tool and gold standard have the same result, divided by the number of cases tested
Analytical specificity	Number of cases where both the new tool and gold standard have a positive finding divided by the number of cases where the gold standard has a positive finding
Analytical selectivity	Number of cases where the new tool and the gold standard have a negative finding divided by the number of cases where the gold standard has a negative finding
Intra-device reliability	Intraclass correlation coefficient of repeated measure taken from the same subjects under the same conditions with the same device
Inter-device reliability	Intraclass correlation coefficient of repeated measure taken from the same subjects under the same conditions with different devices
Clinical accuracy	Number of cases where the new tool correctly predicts the clinical outcome, divided by the number of cases tested
Clinical specificity	Number of cases where the new tool correctly predicts a positive clinical outcome, divided by the number of cases where the clinical outcome is positive
Clinical selectivity	Number of cases where the new tool correctly predicts a negative clinical outcome, divided by the number of cases where the clinical outcome is negative

5.4 Kinematic assessment of bimanual and unimanual reaching

5.4.1 Findings

In Chapter 4 the patient and comparison groups were recorded with optical motion capture during unimanual and bimanual reaching and movements were analysed to determine kinematic parameters. The paretic arm was found to be impaired in terms of movement time, average speed, maximum speed, length index and number of movement units, compared to the non-paretic arm. In other words, reaching with the paretic arm was slower, more fractionated and less direct.

Unlike previous studies of stroke patients, no deficits were found for the ipsilesional arm. This is in contrast to studies of hemispherectomised patients (Dijkerman et al. 2008), patients with unilateral cerebral palsy (Dellatolas et al. 2005) and those with unilateral adult-acquired stroke (Colebatch and Gandevia 1989; Prigatano and Wong 1997). Previous research has also identified abnormal non-paretic arm kinematics in patients with unilateral cerebral palsy (Steenbergen and Meulenbroek 2006) and adult-stroke (Hermsdorfer et al. 1999a; Schaefer et al. 2007; Yarosh et al. 2004).

Differences between this task and that used in other kinematic studies may explain this discrepancy. In other studies participants have been assessed for accuracy (Schaefer et al. 2007; Yarosh et al. 2004). This requirement may have led to differences in the kinematics that were related to the ability to plan and execute an accurate action rather than the reaching task used here that had low accuracy requirements. Other studies have tested different aspects of motor control, including wrist rotation (Yarosh et al. 2004) or fine motor control (Hermsdorfer et al. 1999a). The current study only assessed gross motor control. A difference between the cohort studied by Dijkerman et al. (2008) and that studied here is that in the current study patients were excluded if they could not perform goal-directed reaching. Dellatolas (2005) found that non-paretic arm deficits were only present in 30% of hemiparetic children. Hence, it may be that no effect was found here because of the

exclusion criteria. To test this one could repeat the current assessment on a group of hemispherectomised patients with a greater range of motor abilities.

During bimanual reaching, the patient's arms were desynchronised at movement onset and end and patients often performed bimanual reaches as sequential unimanual actions. The effect decreased over the course of testing, indicating that the impairment might improve with practice. Unlike bimanual synchronisation, spatial interference between the arm trajectories appeared to be preserved. Spatial interference is present in healthy individuals but absent in callosotomised patients. It was speculated that hemispherectomised patients have difficulty controlling both arms simultaneously, but that the inter-cortical network that results in spatial interference may transfer to an intra-cortical network within the remaining hemisphere.

5.4.2 Implications for the ipsilateral control of movement

The kinematic analysis identified two important differences between the patients and comparison group that might be linked to patterns of motor reorganisation. Firstly, it was found that the patients had much lower levels of inter-limb synchronisation than the comparison group. It was hypothesised that, since after hemispherectomy all cortical control must come from one hemisphere, the left and right arms may share neural resources for motor control. This might then encourage patients to lag the movement of one arm relative to the other, so the two arms do not impose simultaneous demands on the same neural areas.

This is speculation, but could be investigated with fMRI. Previous fMRI studies of hemispherectomised patients have concerned themselves with localising the cortical structure that provides motor output to the spinal cord to drive the muscles of the weaker hand (Holloway et al. 2000; Pilato et al. 2009; Rutten et al. 2002; Zsoter et al. 2012). Instead, participants could be tested on a bimanual behavioural task whilst undergoing an fMRI scan, with concurrent recordings of movement onset and end. It would be interesting to

see if trials with greater onset and end lag under the bimanual condition have greater overlap in the neural structures that are active during the task.

Secondly, some patients had lower levels of bimanual spatial interference than the comparison group. In healthy participants, spatial interference is believed to occur due to the inter-hemispheric transfer of motor plans for the left and right limbs via the corpus callosum (Franz et al. 1996a), perhaps due to a bilateral network containing the dorsolateral prefrontal cortex, anterior cingulate, and supramarginal gyrus (Wenderoth et al. 2005). Functional imaging might ask if this network has reorganised to the remaining hemisphere.

5.4.3 Limitations

The kinematic assessment developed for this study had drawbacks, which will be outlined in the following sections.

5.4.4 Systematic ordering of experimental blocks

Participants were asked to perform the task under differing conditions that were administered in the same order for all participants. Differences between the conditions could have been biased by the ordering. For example, since the first round of unimanual conditions preceded the first round of bimanual conditions, if patient declined over time due to fatigue or attentional problems they would have been likely to have performed worse under the bimanual conditions. A standard approach to control for this is to counterbalance the order of the conditions, where each patient would have performed the conditions in a different order.

Counterbalancing was problematic for the experimental design used here. Firstly, since there were eight conditions (each repeated once) there were a large number of different possible orders of the conditions. Since only six patients were studied, neither full counterbalancing nor an inferior approach such as Latin Squares (Reese 1997) would have been possible.

Secondly, one of the factors of interest was differences between the individual patients. If the conditions had been counterbalanced, then any

carry-over effects on the conditions would have varied between the patients. If, for example, patients improved over time and subject 1 was tested with unimanual first and subject 2 was tested with bimanual first then any difference between subjects 1 and 2 in the effect of manuality would have been influenced by the counterbalancing.

Thirdly, counterbalancing does not control for or remove carryover effects (Reese 1997), rather it makes them less predictable. Previous studies have suggested that a better approach is to take these effects under statistical control by including a term in the analysis that accounts for change over time (Baayen et al. 2008). For this reason the trials were indexed and the trial order was included as a term in the model. All effects were therefore calculated after a linear change over time had been controlled for. The statistical model did not account for non-linear effects. This may have occurred due to, for example, exponential changes in attention or interactions between practice effects and fatigue.

Future studies may wish to investigate these issues further. Three possible approaches are: (1) reducing the number of conditions and increasing the number of participants to allow for a counterbalanced approach which can then be compared to the approach used here; (2) including non-linear terms in the model; (3) at the end of each block, asking participants to rate changes in factors that may change over time (e.g. practice, fatigue and attention) to determine if there are likely to be carryover effects. These ratings could also be included in the model.

5.4.5 Analysing sequential reaches as bimanual reaches

Patient participants performed many of the bimanual trials as sequential unimanual reaches. This could have biased the estimated interaction effect between group and manuality, since differences between unimanual and bimanual reaching may not be present when bimanual reaching is performed sequentially. To account for this, the data were reanalysed with sequential reaches excluded. The same conclusions were found, suggesting that the effect of manuality was not significantly biased by this factor. However, this

may not have fully accounted for this difference. A sequential reach is a binary variable, whilst the true difference could be considered continuous. If there is only 10% of overlapping movement of the two arms the trial would not have been considered sequential, but an effect of manuality may have been substantially reduced due to the low level of overlap. Future research may wish to investigate the effect that percent of overlap between the two arms has on the effect of manuality.

5.4.6 Assessing contribution of sensory information to reaching

Chapter 2 demonstrated the significant visual deficits of the patient group. As expected after hemispherectomy all patients had loss of the contralesional hemifield, but also some loss of vision in the residual hemifield, impaired visual acuity and impaired stereopsis at near. These deficits could have large effects on the kinematics of reaching, although previous studies provide contradictory information on the extent to which a simple reaching movement depends on visual feedback. Some studies have found that removing vision through darkening a room or blindfolding has no effect on kinematics (Carella et al. 2003; Jakobson and Goodale 1991; Wing et al. 1986). Others have found movements to be slower when blindfolded (Chieffi and Gentilucci 1993), whilst others have found them to be faster (Jeannerod 1984).

In the current study the contribution of vision was assessed with continuous blindfolding throughout a block of trials. It was found that blindfolding had little effect on their behaviour, suggesting that participants had low dependence on visual feedback when performing the action. However, continuous blindfolding throughout a block meant that participants were required to rely on motor and/or kinaesthetic memory of the target location, which could have biased their behaviour. One could instead remove vision shortly before movement onset, at movement onset or mid-flight. This could be achieved by blacking out the room (Day et al. 1998) or using liquid crystal glasses (Day et al. 2010). Alternatively, instead of experimentally manipulating the task conditions one could include the ratings of the visual assessments in the statistical model. This would mean that: (1) the effect of

visual impairment on reaching kinematics could be estimated, accounting for the variability in visual impairment between patients; (2) the estimated differences between the arms and between unimanual and bimanual reaching would have been computed after controlling for visual impairments.

An important area that was neglected was the role of somatosensory information. As demonstrated by the clinical histories discussed in Chapter 2 and as is known after hemispherectomy (Dijkerman et al. 2008; Holloway et al. 2000), the patients studied here have somatosensory impairments, which can affect movement kinematics (Cardinali et al. 2016). As with vision, future studies may wish to carry out clinical outcome assessments of somatosensory impairments and include these values in statistical modelling of reach kinematics.

5.4.7 Defining reach onset and end

Reach onset and end were defined based on the distance travelled and speed of the forearm. Rather than establishing these values through data analysis they could have been recorded by using sensors. Contact switches could be placed on the table underneath each hand that send triggers when the hands leave the table. Reach end could be recorded for the pressing hand by placing a contact switch on the soap dispenser, which would send a signal when the hand first contacts the soap dispenser plunger. Since the hand that was placed beneath the spout did not contact an object at reach end a contact switch could not be used for this hand. Instead, one could use an infrared sensor could be used that detects when the hand is in this position. Such a setup would need to be tested first to ensure it does not yield false positives.

5.4.8 Alternative interpretations of changes in length index and number of movement units

When the patient group reached with the paretic arm, both the length index and number of movement units were found to be significantly greater than when reaching with the non-paretic, after controlling for the differences between the arms of the comparison group. One could interpret these

differences as reflecting a difficulty in controlling the trajectory of the paretic arm during a functional task. This is not necessarily the case.

Firstly, the primary impairment may have been reduced speed, which in turn affected the trajectory. This seems unlikely due to theoretical reasons – whilst curvature of reaching is known to co-vary with speed, higher speeds are associated with greater curvature (Zago et al. 2018). The increases in length index were present despite the lower speed, suggesting an impairment in both factors.

Secondly, essential tremor is a common symptom after stroke (Siniscalchi et al. 2012). The frequency range of essential tremor is 4-12Hz (Bhatia et al. 2018). If present during reaching this could have led to an increase in the number of acceleration-deceleration phases, hence causing an increase in the number of movement units. Tremor could be removed with high-pass filtering, but the cut-off frequency used here was 20Hz. A more stringent criteria than simply an acceleration followed by a deceleration phase (as has been used elsewhere (Chen et al. 2014; de Oliveira Cacho et al. 2015; Mottet et al. 2017)) was used here: (1) a minimum peak prominence of 20mm/s; (2) a minimum time between two subsequent peaks of 150ms; (3) a minimum peak width of 45ms. The peak width was defined as the time from crossing 50% of the peak prominence during the acceleration phase to crossing 50% of the peak prominence during the deceleration phase. These parameters would still not necessarily mean that tremor components would be ignored though, since essential tremor can be as low as 4Hz. More stringent parameters could have been used, but these may have led to filtering out or ignoring intentional movement phases. One should consider that the results of the Fugl-Meyer Assessment (Chapter 2) indicated that the patients did not have tremor (all patients scored 2 out of 2 on this item). But a more thorough investigation of kinetic tremor could be carried out in future studies to address this potential confound.

Thirdly, motor performance may have been worse if the patients paid less attention during the task or their ability to attend decreased over time.

However, if it is assumed that poorer performance due to difficulties with attention would be present regardless of which arm is being tested, one would expect that patient performance with the non-paretic arm would be worse than the comparison group's dominant arm. Significant differences were not detected between the patient and comparison group when using the dominant/non-paretic arm. Furthermore, the poorer performance of the patient's paretic arm was based on a difference with performance of the non-paretic arm. For these reasons it seems unlikely that poorer performance was a result of difficulties with attention.

5.4.9 Clinical utility of the kinematic assessment

Established approaches for measuring motor function after hemispherectomy include patient, clinician and observer reported outcomes. An advantage of these approaches is that they do not require expensive equipment. In contrast, the kinematic assessment requires expensive technology that is not widely available. Patient reported outcomes have the additional benefit of being direct measures of how a patient feels, which can only be known by asking the patient directly. Clinician and observer reported outcomes are advantageous as they utilise either the clinician's expert understanding of the condition or observations from a person who spends a lot of time with the patient. Examples used in studies of hemispherectomised patients include the Manual Ability Classification System (Hamad et al. 2013), the Actual Amount of Use Test (Bode et al. 2009), the Paediatric Evaluation of Disability Inventory (van Empelen et al. 2004; van Empelen et al. 2005) and the Scales of Independent Behaviour Revised (Basheer et al. 2007). An alternative is to administer a performance outcome assessment, where a patient is scored on a task according to instructions that are administered by a healthcare professional. Performance outcome assessments used in the study of hemispherectomised patients include the Fugl-Meyer Assessment (Bode et al. 2005; Bode et al. 2009; Choi et al. 2010; Liang et al. 2013), the Movement-ABC (van Empelen et al. 2005) and the Gross Motor Function Measure (van der Kolk et al. 2012; van Empelen et al. 2004; van Empelen et al. 2005).

A drawback of clinical outcome assessments is that they rely on a patient or observer's subjective interpretation of the patient's performance. In contrast, the data from the kinematic assessment is acquired by an automated system and analysed with an algorithm. It is possible to increase the reliability of clinical outcome assessments by requiring a high level of clinician training on the assessment, but this increases the administration cost and decreases the availability.

The number of points on the scale of any item is also problematic, since: (1) they may not discriminate between patients with differing levels of ability who fall within the same rating point; (2) two patients who lie just above and below the border of an item's score will receive categorically different ratings and so measurement error can lead to substantially different conclusions (Haas et al. 1996; Hobart et al. 2000; Hobart et al. 2007); (3) it presumes that the differences between each rating of an item is equal, i.e. the difference between 0 and 1 is equal to 1 and 2, and the difference between 0 and 1 for one item is the same as the difference between 0 and 1 for another item (Hobart et al. 2007). Kinematic data is instead acquired on a continuous scale and generally provides performance metrics on a continuous scale (although in this study 'number of movement units' was an exception). This allows for drawing precise differences between patients and tracking precise changes in patient performance over time.

Standard clinical outcome assessments can also be affected by floor or ceiling effects. Where the strength and dexterity of hemispherectomised patients has been assessed previously, all or most patients scored zero on many measures (Dijkerman et al. 2008; Holloway et al. 2000). Due to the precision of kinematic measurements, as long as the patient can perform the task it is possible to quantify a true difference in patient performance whether a group's measurements are very low or high. The results of the current study demonstrate this – it was possible to differentiate between the performance of individual patients on single measures, whilst their scores from single items of the clinical outcome assessments were often the same.

5.4.10 Future evaluation as a performance outcome measure

Before a traditional clinical outcome assessment is accepted it must be validated and be shown to be reliable. A kinematic assessment of motor function should go through a similarly rigorous process. In the sections that follow a proposed plan for evalutating the validity and reliability of the kinematic assessment is set out.

5.4.11 Construct validity

Construct validity is defined as the extent to which an instrument measures the concept of interest. This can be shown by testing for statistical relationships with established measures of the same concept of interest. A major obstacle in establishing the construct validity of the kinematic assessment is that the concept of interest in established clinical outcome assessments is often much broader than the ability to perform functional reaching when seated. The clinical outcome assessments used in this study were the Action Research Arm Test and the Fugl Meyer Assessment. Although the Action Research Arm Test is an established measure of hand and arm function most of the tests require grasp, grip or pinch and hence require hand motor control. In contrast the kinematics assessment was essentially of a gross movement. Three gross movements were assessed with the Action Research Arm Test: placing the hand behind the head, on top of the head or on the mouth. The sum of these scored could then be used to validate the measure. This would not be possible with the dataset acquired here, since all patients scored 2/3 on almost all the gross movement items. Since there was little variability across these items, there would be little value in testing for an association with the kinematic measures. However, the assessments could be carried out on a larger cohort with a greater range of gross motor function.

5.4.12 Test-retest reliability

In the case of an optical motion capture system one can test reliability by capturing multiple measurements with the same system and calculating the intraclass correlation coefficient. Similarly, reliability can be assessed by

calculating the intraclass correlation coefficient for measurements taken by two different optical motion capture systems from the same subject under the same conditions. Previous studies have found that repeated measurements taken with a system produced by the same manufacturer as the system used in this study have high reliability for gait (Rusaw et al. 2017) and jaw movements (Calixtre et al. 2017). However, the reliability of this system to capture the specific measurements types within the context of the task used here has not been established. To do so, the intraclass correlation coefficient could be calculated on measurements captured from the same set of participants in two different sessions (Koo and Li 2016). To test the extent to which the measurements were dependent on the type of system, the intraclass correlation coefficient could be calculated on measurements captured by different systems.

5.4.13 Ability to detect change

The kinematic assessment could be used in a rehabilitation setting to detect change over time. If so, the assessment should be evaluated in terms of its minimal detectable change and minimal clinically important change. Minimal detectable change is defined as the minimum amount of change in a measure that is required to be confident that the difference reflects true change and not measurement error (Korakakis et al. 2014; Nair et al. 2012). To calculate minimal detectable change, one first calculates the Standard Error of Measurement (SEM) to measure within-subject variability. Minimal detectable change can then be calculated as 1.96 x SEM x square root of 2. Minimal clinically important change is the smallest amount of change in a measure that might be considered important by a patient or clinician (Lehman and Velozo 2010). This can be evaluated by taking a self-report of the patient's perception of change in their function (from worse to better) after an intervention and then calculating the minimum change in the kinematic measure from before to after that maximises the sensitivity or specificity to predict the patient rating.

5.4.14 Further development

For movement analysis, a choice was made to focus on one task that all participants could perform and then analyse the effects of varying task conditions on a set of kinematic variables. This leaves open many other avenues for further motion capture research. Firstly, since participants have such difficulty with fine motor control, the task was a gross motor action. Other studies might investigate other gross movements and test the effect of increasing the sensory, cognitive or motor demands. It would also be of interest to investigate fine motor control. For the weaker arm, given the severe deficits of most patients, it might be necessary to limit this to single case studies. A particularly interesting approach, though, might be to test the fine motor control of the stronger upper limb. In the current study, the only impairment of the stronger side was found in C.B. on the Action Research Arm Test for fine motor control. Dijkerman et al. (2008) also found significant differences between patients and controls in terms of dexterity testing. As long as the cognitive demands of the task were low, most patients might be able to participate in testing of just the stronger arm (although behavioural issues may necessitate excluding some) and this might then yield a large sample size.

Secondly, as discussed above, there are many further issues that could be investigated in terms of vision. The Ophthalmology Department carried out a detailed assessment of each patient's vision and so a particularly fruitful collaboration might be sought where these insights were used in the further development of the current kinematics task.

Thirdly, hemiparesis is known to be associated with deficits in abnormal motor synergies and the breakdown of individual joint control (Dewald and Beer 2001; Dewald et al. 1995; Sukal-Moulton et al. 2014; Sukal-Moulton et al. 2013). The results of the Fugl-Meyer Assessment confirmed that this motor control issue is a concern too for hemispherectomised patients. This issue was not pursued here with kinematic analysis. A further issue is the effect that hemispherectomy has on movement synergies. It is known, for

example, that spasticity can be reduced by the operation (Krynauw 1950; Zülch and Micheler 1978). It might also affect other imbalances in the nervous system, with implications for motor control.

In order to investigate this, patients could be assessed before and after hemispherectomy. If so, two important factors should be considered. Firstly, the age of surgical candidates ranges from infancy to late teens, making the choice of an appropriate motor task difficult. Secondly, participants may have no functional use of the arm before surgery or may lose all functional use after. Kinematic testing of the weaker arm of these patients would therefore not be possible.

In addition to further kinematic research, some of the issues highlighted in this thesis could be addressed with standard behavioural testing. One of the findings of this project was that the patient group exhibited lowers level of bimanual, spatial interference than the healthy, comparison group. The measure used here – curvature of the trajectory – provided a measure of spatial interference in an everyday functional task. What was not established, though, was whether the patients exhibited sub-normal levels of spatial interference on classical tests, such as simultaneous circle and line drawing. Before proceeding with more complex investigations, it would be worthwhile assessing the patients on these classical tests and comparing the results to both the kinematic analysis and previous investigations of callosotomised patients.

5.5 Limitations of the participant selection criteria

Patients were excluded from the study if they were unable to perform goal-directed reaching with the weaker arm. Given the extreme motor deficits of this patient group, the bar was intentionally set low, with this action considered a very basic, daily function of the upper limbs. Nonetheless, this means that the results cannot be generalised to the population of hemispherectomised patients, some of whom have no functional use of the paretic arm (Wilson 1970). This point, together with the rarity of the disease and its treatment, also meant that the sample size was very small, although

not dissimilar to other studies of hemispherectomised patients which is often single case research. Secondly, the clinical history of patients was inconsistent, with the types and number of repetitions of sensory and motor testing varying between patients. Clinical research would benefit from a consistent, long-term approach to assessing patients before and after surgery.

The comparison group was matched to the patients in terms of sex (patient group = three male, three female; comparison group = six male, six female) and age (patient group = 20-36 years; comparison group = 19-37 years). The comparison group was not matched in terms of handedness. The patient group were all left-handed except for one patient who was right-handed. Children with childhood onset hemiplegia are forced to use the ipsilesional limb for most functional tasks. The ipsilesional side is therefore considered the “dominant” side, but one cannot be sure that the contralesional limb would have been dominant if hemiplegia began after the development of hand dominance. All but one of the patients here developed hemiplegia in their first year (for the exception, onset of hemiplegia was unknown but seizure onset was 8 months and hemispherectomy took place at 2 years, 8 months). Since there was no clear case for considering the patients as right handers who were forced to switch hand dominance, or simply left handers, the comparison group was not selected based on handedness.

The comparison group was not matched by visual impairment. As discussed previously, visual impairment may have affected task performance on the kinematic task, though blindfolding had little effect on their performance, suggesting that participants had low dependence on visual feedback when performing the action. To further control for visual impairment future studies may attempt to match the comparison group. Alternatively, all participants could be assessed with the visual tests of Chapter 2 and these scores could then be included as terms in the statistical models. The comparison group was not matched for IQ either, however the task was a simple task that could be easily understood by the patients and so it was considered unlikely that this would have affected their motor performance. Furthermore, if IQ did have

an effect on patient kinematics, this should have been present in the kinematics of both arms, but the kinematics of the non-paretic arm were not significantly different to the comparison group.

5.6 Conclusions

This research project set out to consider two forms of upper limb assessment that could complement those currently used for hemispherectomised patients. A novel kinematic assessment was developed and shown to be feasible for identifying deficits in motor control. This method demonstrated impairments in the speed, fractionation and efficiency of contralesional arm movement. Movement of the stronger arm was unimpaired though – this differs from studies of patients with unilateral stroke. It was also demonstrated that there is a breakdown in the synchronisation of bimanual movement and increased tendency to perform bimanual tasks as sequential unimanual actions. This could be due to the demands of controlling the simultaneous movement of both limbs with one hemisphere. A neurophysiological assessment was applied to test for the existence of a functional ipsilateral pathway. In patients with superior motor function, motor drive to left and right wrist muscles was shown to receive common drive, indicative of a functional ipsilateral pathway. This could be due to the preservation of ipsilateral corticospinal pathways that are typically pruned during development. This method could be used for pre-surgical evaluation of motor plasticity. It is suggested that pre- and post- surgical motor assessments would be improved by the inclusion of both methods. To achieve this, the approaches would now need to be validated in a larger cohort of patients.

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7. Appendices

7.1 Normative values for dynamometry testing

Grip	Lower Age	Upper Age	Sex	Hand	*Mean* (kg)	*SD* (kg)
Power	20	24	Male	Dominant	54.88	9.34
Power	20	24	Male	NonDominant	47.40	9.89
Power	25	29	Male	Dominant	54.79	10.43
Power	25	29	Male	NonDominant	50.12	7.35
Power	30	34	Male	Dominant	55.25	10.16
Power	30	34	Male	NonDominant	50.08	9.84
Power	35	39	Male	Dominant	54.29	10.89
Power	35	39	Male	NonDominant	51.21	9.84
Power	40	44	Male	Dominant	52.98	9.39
Power	40	44	Male	NonDominant	51.17	8.48
Power	45	49	Male	Dominant	49.85	10.43
Power	45	49	Male	NonDominant	45.72	10.34
Power	50	54	Male	Dominant	51.53	8.21
Power	50	54	Male	NonDominant	46.22	7.71
Power	55	59	Male	Dominant	45.86	12.11
Power	55	59	Male	NonDominant	37.74	10.61
Power	60	64	Male	Dominant	40.69	9.25
Power	60	64	Male	NonDominant	34.84	9.21
Power	65	69	Male	Dominant	41.32	9.34
Power	65	69	Male	NonDominant	34.84	8.98
Power	70	74	Male	Dominant	34.16	9.75
Power	70	74	Male	NonDominant	29.39	8.21
Power	20	24	Female	Dominant	31.93	6.58
Power	20	24	Female	NonDominant	27.67	5.94

Grip	Lower Age	Upper Age	Sex	Hand	*Mean* (kg)	*SD* (kg)
Power	25	29	Female	Dominant	33.79	6.30
Power	25	29	Female	NonDominant	28.80	5.53
Power	30	34	Female	Dominant	35.70	8.71
Power	30	34	Female	NonDominant	30.84	8.03
Power	35	39	Female	Dominant	33.61	4.90
Power	35	39	Female	NonDominant	30.07	5.31
Power	40	44	Female	Dominant	31.93	6.12
Power	40	44	Female	NonDominant	28.26	6.26
Power	45	49	Female	Dominant	28.21	6.85
Power	45	49	Female	NonDominant	25.40	5.76
Power	50	54	Female	Dominant	29.85	5.26
Power	50	54	Female	NonDominant	25.99	4.85
Power	55	59	Female	Dominant	25.99	5.67
Power	55	59	Female	NonDominant	21.45	5.40
Power	60	64	Female	Dominant	24.99	4.58
Power	60	64	Female	NonDominant	20.73	4.58
Power	65	69	Female	Dominant	22.50	4.40
Power	65	69	Female	NonDominant	18.60	3.72
Power	70	74	Female	Dominant	22.50	5.31
Power	70	74	Female	NonDominant	18.82	4.63
Key pinch	20	24	Male	Dominant	11.79	1.59
Key pinch	20	24	Male	NonDominant	11.25	1.54
Key pinch	25	29	Male	Dominant	12.11	2.22
Key pinch	25	29	Male	NonDominant	11.34	2.00
Key pinch	30	34	Male	Dominant	11.97	2.18
Key pinch	30	34	Male	NonDominant	11.88	2.31
Key pinch	35	39	Male	Dominant	11.84	1.45

Grip	Lower Age	Upper Age	Sex	Hand	*Mean* (kg)	*SD* (kg)
Key pinch	35	39	Male	NonDominant	11.61	1.77
Key pinch	40	44	Male	Dominant	11.61	1.18
Key pinch	40	44	Male	NonDominant	11.39	1.81
Key pinch	45	49	Male	Dominant	11.70	1.77
Key pinch	45	49	Male	NonDominant	11.25	2.00
Key pinch	50	54	Male	Dominant	12.11	2.00
Key pinch	50	54	Male	NonDominant	11.84	1.91
Key pinch	55	59	Male	Dominant	10.98	1.91
Key pinch	55	59	Male	NonDominant	10.43	2.13
Key pinch	60	64	Male	Dominant	10.52	2.45
Key pinch	60	64	Male	NonDominant	10.07	1.86
Key pinch	65	69	Male	Dominant	10.61	1.77
Key pinch	65	69	Male	NonDominant	9.98	1.63
Key pinch	70	74	Male	Dominant	8.75	1.09
Key pinch	70	74	Male	NonDominant	8.71	1.36
Key pinch	20	24	Female	Dominant	7.98	0.91
Key pinch	20	24	Female	NonDominant	7.35	0.95
Key pinch	25	29	Female	Dominant	8.03	0.95
Key pinch	25	29	Female	NonDominant	7.53	0.95
Key pinch	30	34	Female	Dominant	8.48	1.36
Key pinch	30	34	Female	NonDominant	8.07	1.63
Key pinch	35	39	Female	Dominant	7.53	0.91
Key pinch	35	39	Female	NonDominant	7.26	1.22
Key pinch	40	44	Female	Dominant	7.57	1.41
Key pinch	40	44	Female	NonDominant	7.17	1.41
Key pinch	45	49	Female	Dominant	7.98	1.45
Key pinch	45	49	Female	NonDominant	7.53	1.32

Grip	Lower Age	Upper Age	Sex	Hand	*Mean* (kg)	*SD* (kg)
Key pinch	50	54	Female	Dominant	7.57	1.13
Key pinch	50	54	Female	NonDominant	7.30	1.22
Key pinch	55	59	Female	Dominant	7.12	1.13
Key pinch	55	59	Female	NonDominant	6.67	1.00
Key pinch	60	64	Female	Dominant	7.03	1.22
Key pinch	60	64	Female	NonDominant	6.40	1.13
Key pinch	65	69	Female	Dominant	6.80	1.18
Key pinch	65	69	Female	NonDominant	6.49	1.27
Key pinch	70	74	Female	Dominant	6.58	1.32
Key pinch	70	74	Female	NonDominant	6.26	1.36
Power	6	7	Male	Dominant	14.74	2.18
Power	6	7	Male	NonDominant	13.93	2.45
Power	8	9	Male	Dominant	19.01	3.36
Power	8	9	Male	NonDominant	17.69	4.22
Power	10	11	Male	Dominant	24.45	4.40
Power	10	11	Male	NonDominant	21.95	4.90
Power	12	13	Male	Dominant	26.63	7.03
Power	12	13	Male	NonDominant	25.13	7.67
Power	14	15	Male	Dominant	35.06	6.99
Power	14	15	Male	NonDominant	29.21	6.76
Power	16	17	Male	Dominant	42.64	8.80
Power	16	17	Male	NonDominant	35.61	8.66
Power	18	19	Male	Dominant	48.99	11.16
Power	18	19	Male	NonDominant	42.18	12.61
Power	6	7	Female	Dominant	12.97	2.00
Power	6	7	Female	NonDominant	12.29	2.00
Power	8	9	Female	Dominant	16.01	3.76

Grip	Lower Age	Upper Age	Sex	Hand	*Mean* (kg)	*SD* (kg)
Power	8	9	Female	NonDominant	14.97	3.13
Power	10	11	Female	Dominant	22.54	3.67
Power	10	11	Female	NonDominant	20.50	3.08
Power	12	13	Female	Dominant	25.76	4.81
Power	12	13	Female	NonDominant	23.09	5.40
Power	14	15	Female	Dominant	26.35	5.58
Power	14	15	Female	NonDominant	22.36	5.40
Power	16	17	Female	Dominant	30.53	7.48
Power	16	17	Female	NonDominant	25.81	6.35
Power	18	19	Female	Dominant	32.48	5.58
Power	18	19	Female	NonDominant	27.99	5.67
Key pinch	6	7	Male	Dominant	5.13	0.91
Key pinch	6	7	Male	NonDominant	4.81	0.95
Key pinch	8	9	Male	Dominant	5.94	1.18
Key pinch	8	9	Male	NonDominant	5.53	1.13
Key pinch	10	11	Male	Dominant	6.94	1.41
Key pinch	10	11	Male	NonDominant	6.58	1.32
Key pinch	12	13	Male	Dominant	7.53	1.32
Key pinch	12	13	Male	NonDominant	7.08	1.27
Key pinch	14	15	Male	Dominant	9.48	1.72
Key pinch	14	15	Male	NonDominant	9.03	1.68
Key pinch	16	17	Male	Dominant	10.57	1.54
Key pinch	16	17	Male	NonDominant	9.89	1.63
Key pinch	18	19	Male	Dominant	10.66	1.86
Key pinch	18	19	Male	NonDominant	10.39	1.81
Key pinch	6	7	Female	Dominant	4.35	0.68
Key pinch	6	7	Female	NonDominant	4.13	0.68

Grip	Lower Age	Upper Age	Sex	Hand	*Mean* (kg)	*SD* (kg)
Key pinch	8	9	Female	Dominant	5.26	1.18
Key pinch	8	9	Female	NonDominant	5.13	0.95
Key pinch	10	11	Female	Dominant	6.44	0.95
Key pinch	10	11	Female	NonDominant	6.03	0.91
Key pinch	12	13	Female	Dominant	6.89	1.18
Key pinch	12	13	Female	NonDominant	6.40	1.36
Key pinch	14	15	Female	Dominant	7.08	1.13
Key pinch	14	15	Female	NonDominant	6.71	1.22
Key pinch	16	17	Female	Dominant	7.85	1.36
Key pinch	16	17	Female	NonDominant	7.53	1.41
Key pinch	18	19	Female	Dominant	8.21	1.09
Key pinch	18	19	Female	NonDominant	7.80	1.13

7.2 Principles of regression analysis

7.2.1 Gauss-Markov assumptions

For a multiple regression procedure to be unbiased in its estimators the model error must be random across repeated sampling. One can select between many different unbiased methods of linear modelling. Since the aim of the model is to produce a precise estimator, the method that is considered the *best* estimator is that which minimises the variance between the model and the explained variable.

Under the Gauss-Markov assumptions *linear in the parameters*, *random sampling*, *no collinearity* and *zero conditional mean*, detailed below, ordinary least squares (OLS) regression provides unbiased estimators. Under the Gauss-Markov assumption of *homoscedasticity*, it is the *best* linear unbiased estimator (BLUE). In order to test hypotheses about a particular estimator in a model that has been generated by OLS regression, we must also know its sampling distribution. OLS assumes *normality*. Under these assumptions, then, OLS is the method of choice.

It is the aim of this section to identify procedures that can be adopted when one or more of these assumptions are violated. As will be discussed, certain violations can be avoided by transforming the data prior to fitting. Alternatively, a different model may be used: a random effects term may be added; a different covariance structure may be assumed; a weighting factor may be included; a different sampling distribution may be assumed. These variations may require that a different fitting method be used, such as maximum likelihood (ML), restricted maximum likelihood (REML) or restricted maximum pseudo likelihood (REMPL) estimation. The theoretical reasons for the choice of fitting method are beyond the scope of this thesis and were chosen on the basis of convention.

7.2.2 Linear in the parameters

Firstly, it is assumed that the model in the population is linear in the parameters:

$$y = B_0 + B_1 x_1 + B_2 x_2 + \cdots + B_k x_k + u$$

, where B_0, B_1 ... B_k are the unknown parameters (constants) of interest and u is an unobservable random error. The model should be linear in the parameters B_0, B_1 ... B_k.

The relationship between the explained and explanatory variables may be non-linear if, for example, it is exponential or there is a floor or ceiling effect. If one attempts to use a linear method when the relationship between the explained variable and the explanatory variables is non-linear, then the linear model will be unable to account for at least some aspect of the non-linear relationship and this will produce a systematic bias. Plotting the residuals of the model against the fitted values allows one to informally detect violations of this assumption by asking if a non-linear pattern is present.

If the data type leads one to expect a non-linear relationship, then one should consider applying a mathematical transformation to the data prior to fitting the model. For example, if the value of the explained variable is expected to decrease at a rate proportional to the set of explanatory variables, one could apply a logarithmic transformation to the explained variable before proceeding with a linear regression model. If all assumptions hold for the transformed data, OLS remains the BLUE.

If it is not possible to cast the model in linear parameters on either untransformed or transformed data, one may consider using non-linear regression, where the explained variable is modelled as a combination of a function of the non-linear parameters and the explanatory variables. One approach, generalised linear modelling, is discussed below.

It is further assumed that the population error u is independent of the explanatory variables x_1, x_2 ... x_k and is normally distributed with zero mean and variance:

$$\sigma^2 : u \sim Normal(0, \sigma^2)$$

If the error term is normally distributed, then the sampling distributions of the estimators are normally distributed, any linear combination of the estimators is normally distributed and any subset of the estimators has joint normal distribution. This assumption therefore allows us to derive *t* statistics about a particular estimator and hence derive *p* values. Violations of normality often arise if the distribution of one or more explained or explanatory variables is not normally distributed and/or the relationship between them is not linear. To test the assumption of normality informally one can plot a histogram of the residuals. If the assumption has been violated, one can follow the same procedure for non-linear relationships.

One option for dealing with non-linear relationships is to fit a generalised linear model. Linear regression and generalised linear regression differ along two lines. Firstly, a linear regression model assumes that, at each set of values for the explanatory variables, the explained variable has a normal distribution with mean μ. A generalised linear regression model assumes that, at each set of values for the explanatory variables, the explained variable has one of a variety of distributions, with parameters including a mean μ. The expected distribution is specified when fitting the model. Secondly, although both linear regression and generalised linear regression compute a coefficient vector *b* that defines a linear combination *Xb* of the explanatory variables *X*, linear regression models μ as *Xb*, whilst generalised linear regression applies a mathematical link function *f* to μ, so that $f(\mu)$ is modelled as *Xb*. The link function is specified when fitting the model. Possible link functions include simply *identity*, where no transformation is assumed, or *log*, where the linear combination of explanatory variables *Xb* is assumed to have a relationship with the natural logarithm of the mean explained variable μ.

A generalised linear model can be an effective method when dealing with a limited explained variable, i.e. one whose range of values is substantively restricted, such as a binary variable, a percentage or a count variable. For example, applications that involve counting the number of times a random

event occurs in a given amount of time are known to often form a Poisson distribution. One may therefore find that a generalised linear regression model, which assumes that, at each set of values for the explanatory variables, the explained variable has a Poisson distribution, may provide a better fit.

7.2.3 Random sampling

It is assumed that the data are a random sample of n independent observations with normal errors,

$$\{(x_{i1}, x_{i2}, \dots, x_{ik}, y_i) : i = 1, 2, \dots, n\}$$

That each observation is independent is reflected in the model's standard covariance structure. When repeated measures are taken per subject/unit, the assumption is not satisfied, since one would expect correlation between observations within each unit. This fact can be incorporated into the linear model by adding a variable – a *random effects* term – that groups observations. A model that contains both fixed effects (conventional regression terms) and random effects is termed a mixed effects model. In a mixed effects model, random variation between units is still assumed, as reflected in a standard covariance structure, but it is also assumed that observations within each unit are correlated. This is reflected in the model by specifying a different structure for covariance between observations within a unit. The choice of which covariance structure to use should depend on the experimental design and model terms. If it is assumed that correlation between measurements is constant within each unit, then a compound symmetry covariance structure should be used. However, if one trial has a carry-over effect on the next, but one that decays over time, correlation between observations will vary within each unit. If this relationship existed, but was not accounted for in the model, then the residual values would correlate with the lagged residual values. This can be detected by plotting the residual value at t against the residual value at $t - 1$ and asking if the two

are correlated. If so, an autoregressive covariance structure may be more appropriate.

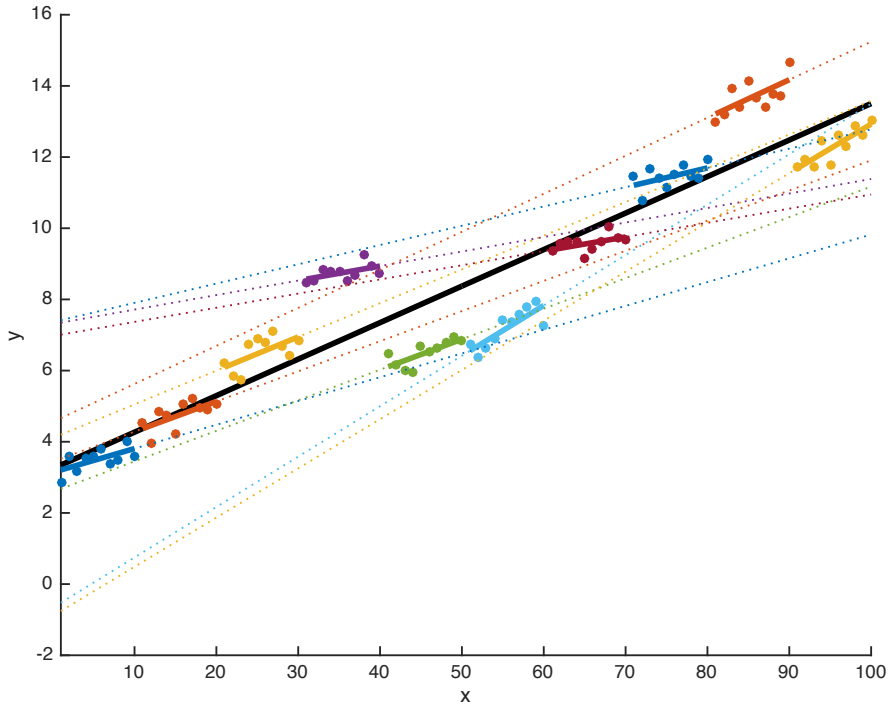


Figure 26. Random intercept and slope model

In a random intercepts and slopes model, a different intercept and slope is calculated for each unit. In the plot, the black line represents the estimated slope for all observations. Each colour grouping represents a different unit and coloured lines represent estimated slopes for each unit. In this data the estimated slopes differ between units but are similar to the slope for all observations. There is a greater difference between units, though, in terms of intercepts.

A random effects term can be supplied to a regression model as a random intercepts term or a random slopes term. In a model with fixed effects only, the intercept is calculated as the mean value of the observations when the value of the fixed effects term is zero. In a model with both a fixed effect and random intercepts term, one coefficient is estimated for the fixed effect across all units, but a separate intercept is calculated for each unit, as the mean value of the observations within that unit when the value of the fixed

effects term is zero. This means that the variance in the model is partitioned into two components. Firstly, there is the variance between the observations within each unit, after controlling for the fixed effect. Secondly, there is the variance between the units themselves, after controlling for the fixed effect. In a model with both a fixed effect and a random slopes term, separate coefficients for the fixed effect are estimated for each unit, but one intercept is calculated, as the mean value of all observations when the value of the fixed effect term is zero. Alternatively, a model may supply terms for fixed effects, random intercepts and random slopes. In this case, both separate coefficients for the fixed effect are calculated for each unit and separate intercepts for each unit. For an illustration, see Figure 26.

Both units and observations are considered samples from a population. For example, if one is analysing six sets of exam results from 100 different pupils, with each set taken from a different school, a random effects term might be included that specifies the school from which the exam results were taken. The six schools are considered random samples from the population of all schools, whilst the exam results within each school are considered random samples of the exam results of all pupils within that school. If the p-value of a random effects term (intercept or slope) is below the significance threshold this suggests that, after controlling for the fixed effect(s), there is significant variation between the units in the estimate of this effect. In the schools example, this would indicate that there was significant variation between schools in terms of exam results. The random effects term may then be considered at the level of the unit by asking if the estimated intercept or slope for any unit, after controlling for all fixed effect(s), is significantly different to zero. In the schools example, a school's intercept that was estimated to be significantly greater than zero, after controlling for fixed effects, would indicate that the mean exam score for that school was estimated to be greater than the other schools. Rather than just providing the mean effect, this approach estimates inter-individual differences.

7.2.4 No perfect collinearity

It is assumed that in the sample (and therefore in the population), none of the explanatory variables is constant and there are no exact linear relationships (perfect collinearity) among the explanatory variables.

This assumption can be violated if an explanatory variable is accidentally included in the model twice, an explanatory variable is a constant multiple of another or an explanatory variable is an exact linear function of two or more other explanatory variables. For example, if the explanatory variables include the duration that an object was moving, its mean velocity and the distance it has travelled then, since the mean velocity is the duration divided by the distance, there would exist an exact linear relationship within the explanatory variables and the inclusion of all three would violate the assumption of *no perfect collinearity*. To avoid violating this assumption one can simply exclude one of the problematic explanatory variables from the model.

7.2.5 Zero conditional mean

It is assumed that the error u has an expected value of zero given any values of the explanatory variables, i.e.

$$\mathrm{E}(u|x_1, x_2, \dots, x_k) = 0$$

This assumption can be violated if the relationship between the explained and explanatory variables is not linear and/or if an important explanatory variable has been omitted. Plotting the residuals of the model against the fitted values allows one to informally detect violations of this assumption by asking if the residuals are approximately evenly distributed around zero. If the assumption has been violated one should consider if the model could be improved by adding another explanatory variable. Otherwise it may be more appropriate to treat the relationship as non-linear and employ one of the approaches discussed under the assumption *linear in the parameters*.

7.2.6 Homoscedasticity

OLS assumes that the error u has the same variance given any values of the explanatory variables, i.e.

$$Var(u|x_1 \dots x_k) = \sigma^2$$

Constant variance is termed 'homoscedasticity' and its antonym is heteroscedasticity. If variance is not constant then it tends to be underestimated, leading to overly liberal significance tests. As with the assumption *zero conditional mean*, the assumption of homoscedasticity can be violated if the relationship between the explained and explanatory variables is not linear and/or if an important explanatory variable has been omitted. Heteroscedasticity can be detected by plotting the residual values against the fitted values. The variance of the residuals should remain constant across the fitted values.

The methods of dealing with a violation of this assumption include those listed under *zero conditional mean*. Another option, if all other assumptions have been met, is to use a weighted least squares (WLS) procedure rather than OLS, where an additional weighting factor is included in the fitting process. The weighting factor determines how much each explanatory value influences the estimated value by assigning greater weight to data points with low estimated error.

7.2.7 Outliers and influential observations

The definition of an outlier can be vague, but here the term is used to refer to data points that have a relatively large effect on a regression model by affecting the regression slope, regression intercept and/or assessment of the model. If an outlier affects the slope it is referred to as an influential point, though even if the slope is unaffected an outlier may still influence the assessment of the model.

A model's coefficient of determination (R^2) indicates how well a statistical model fits the observations. It is calculated as:

$$R^2 = 1 - \frac{SS_{\mathrm{E}}}{SS_{\mathrm{T}}}$$

, where SS_{E} is the sum of squares of the residuals and SS_{T} is the total sum of squares. If an observed value lies close to the regression slope, then it will have little effect on the residuals and so little effect on SS_{E}. However, if it is also far from the mean of all observed values, then it will increase SS_{T} and, as a result, decrease R^2. On the other hand, if an observed value lies far from the regression slope but close to the mean of all observed values, then whilst it will have little effect on the residuals and SS_{T}, it will increase SS_{E} and consequently increase R^2. Alternatively, if an observed value lies far from the regression slope and far from the mean of all observed values, then the values of both SS_{E} and SS_{T} will be increased by its inclusion, whilst the effect on R^2 will depend on its relative effects on SS_{E} and SS_{T}. For these reasons, a linear regression model works on the assumption that the exclusion of any individual observation or small subset of observations will not have a large effect on SS_{E} or SS_{T}. However this assumption can be violated if an observation is present that has a value that is far from the mean and/or has a large residual value.

Various methods can be used to identify outliers. One possibility is to plot and visually inspect the values of the explained variable or residuals and identify potential outliers based on their proximity to the mean or median. In the context of a box-plot, outliers are often defined as $> Q_3 + (1.5 \times (Q_3 - Q_1))$ or $< Q_1 - (1.5 \times (Q_3 - Q_1))$, where Q_1 and Q_3 are the first and third quartiles of the data, respectively. Once any outliers have been identified, one must decide how to proceed with analysis. Outliers may occur due to an error (e.g. measurement error; sampling error) or be a legitimate observation. If an error has occurred, then it may be necessary to re-process the data or exclude those observations from analysis. However, if the observation were a legitimate case, then an analysis that excludes this observation would not be a true reflection of the data. In this case, as with heteroscedasticity, one may choose to transform the data or use a robust fitting method. Alternatively, or if

these methods have already been applied, one might report the model estimates with and without the outliers.

7.2.8 Dummy variables

When a regression model includes binary conditions as dummy variables, the coefficients can be interpreted with respect to a set of reference conditions. We may for example, compare the effect of sex and handedness on typing speed, by selecting the reference level of sex to be female and handedness to be left. The main effect of sex, then, estimates the difference between left handed women (the reference) and left handed men. The main effect of handedness estimates the difference between left handed women and right handed women. The interaction between sex and handedness estimates the difference between left handed women and right handed men that occurs in addition to the estimates of the main effects.

7.3 Diagnostic plots

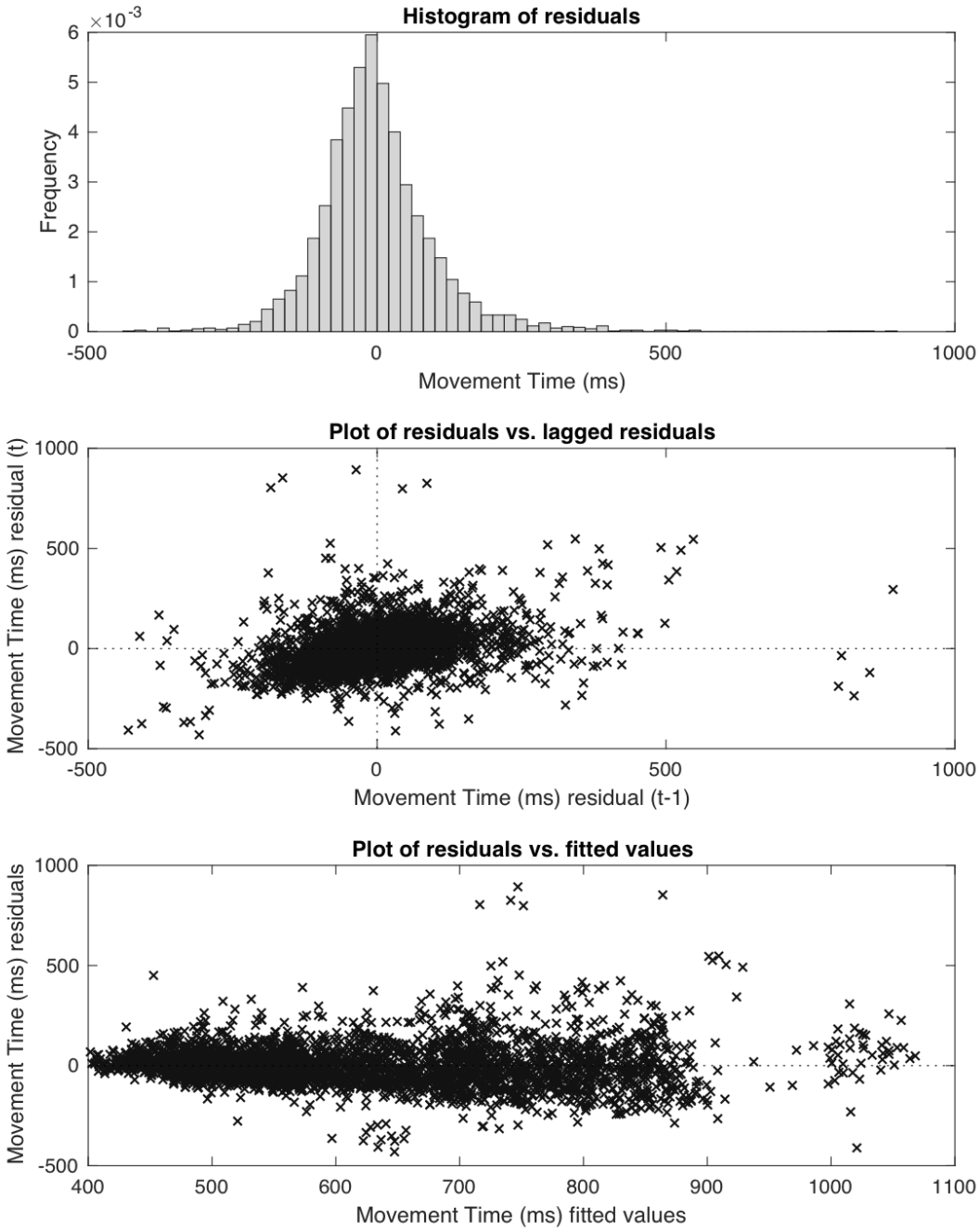


Figure 27. Residuals, movement time

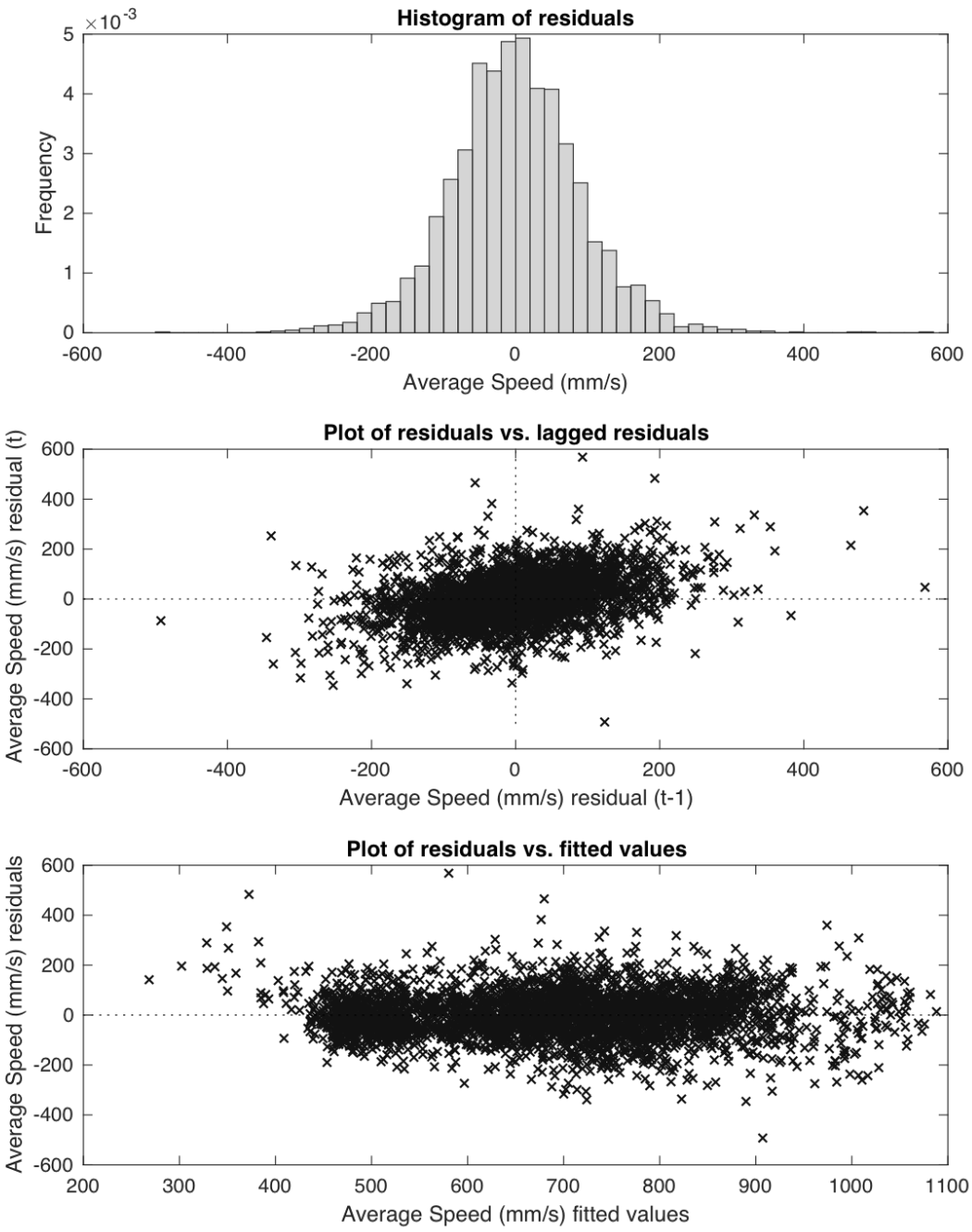


Figure 28. Residuals, average speed

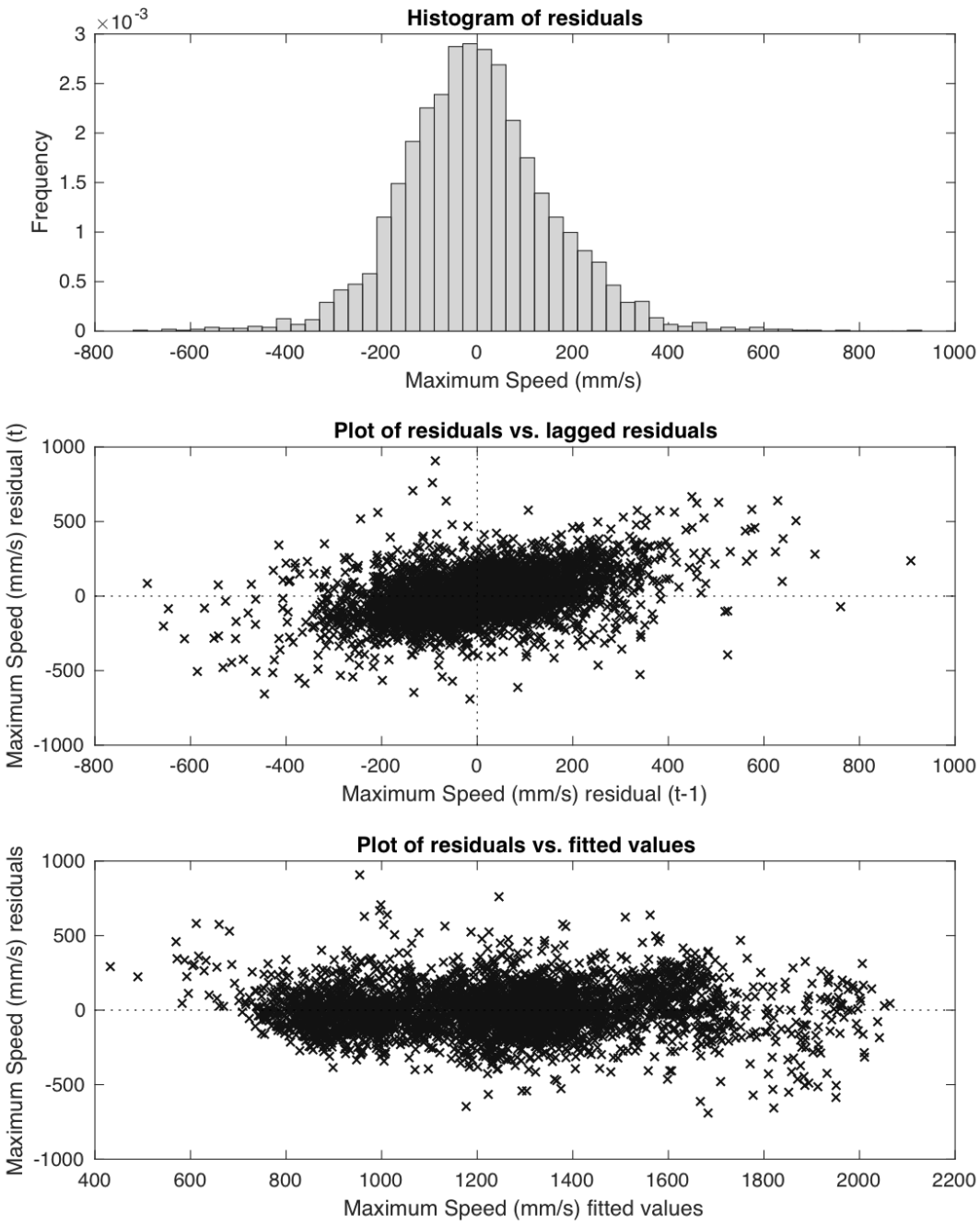


Figure 29. Residuals, maximum speed

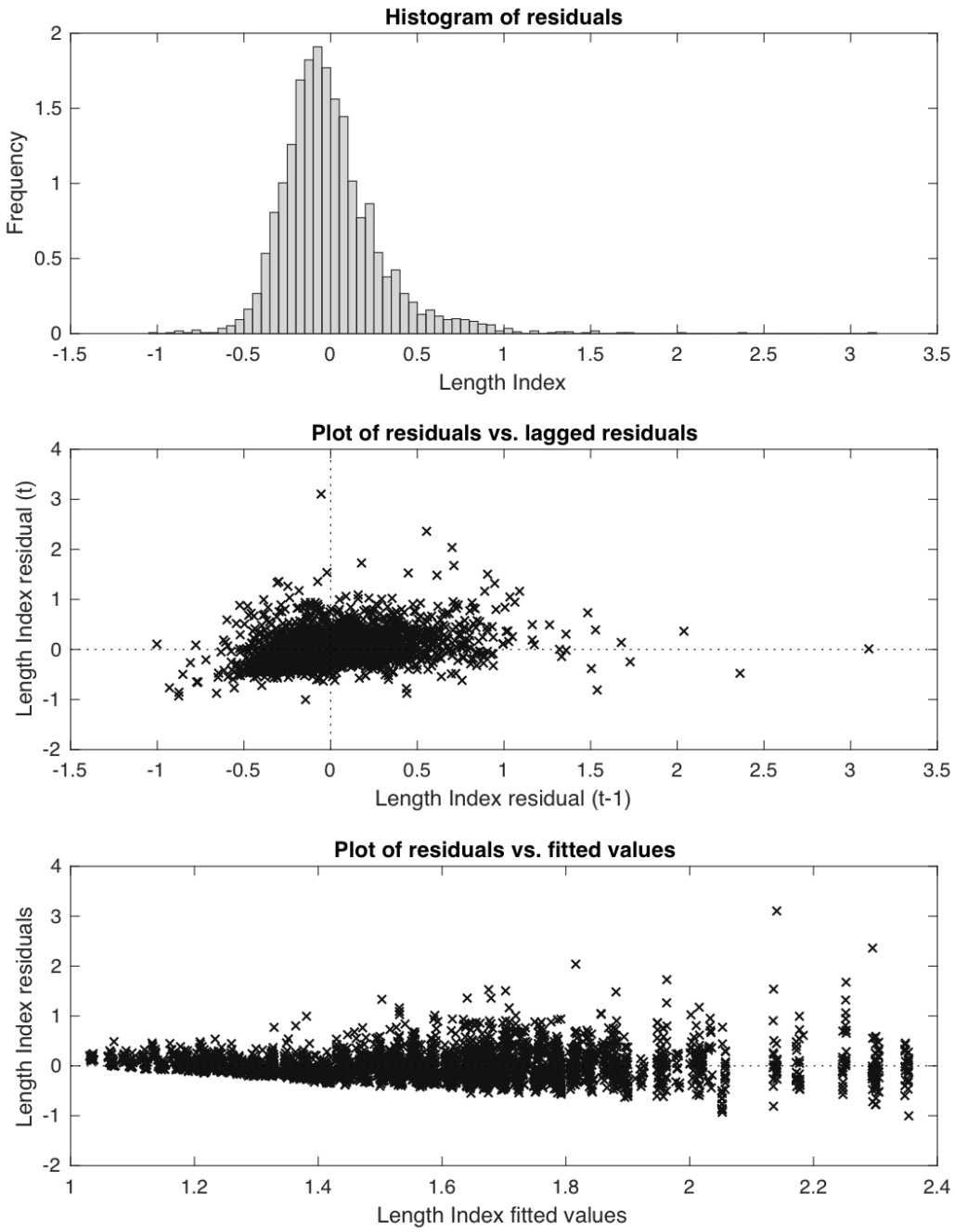


Figure 30. Residuals, length index

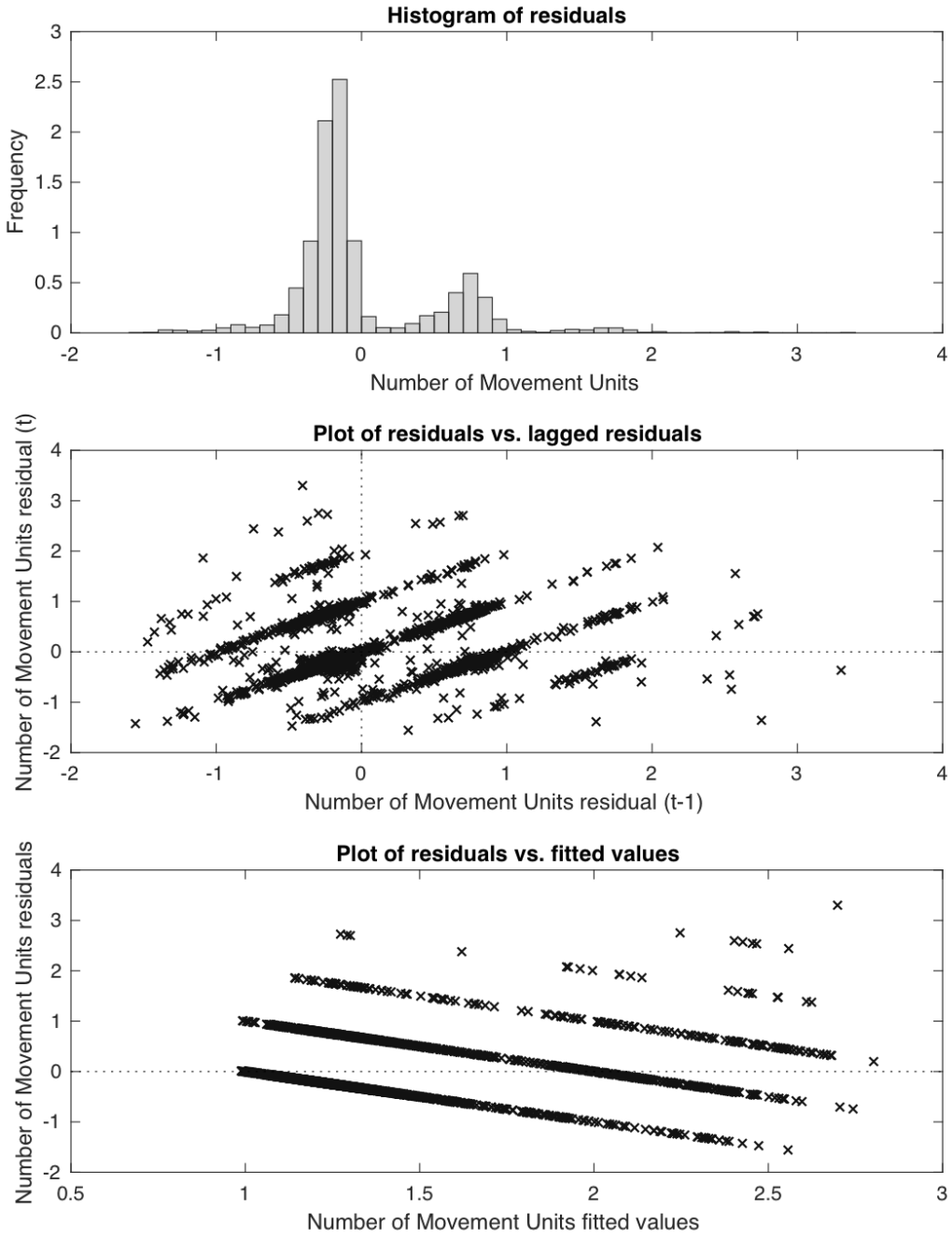


Figure 31. Residuals, number of movement units

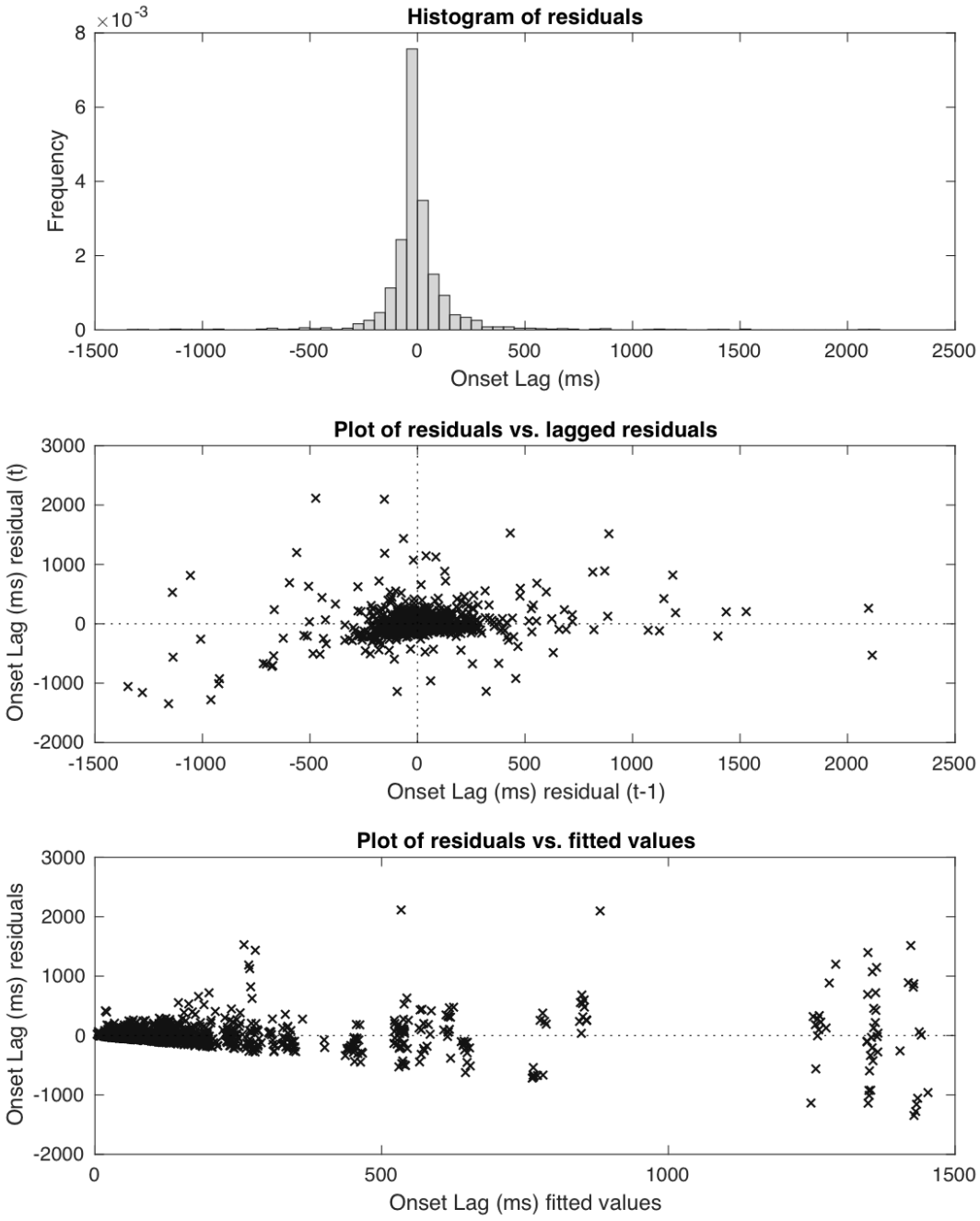


Figure 32. Residuals, onset lag

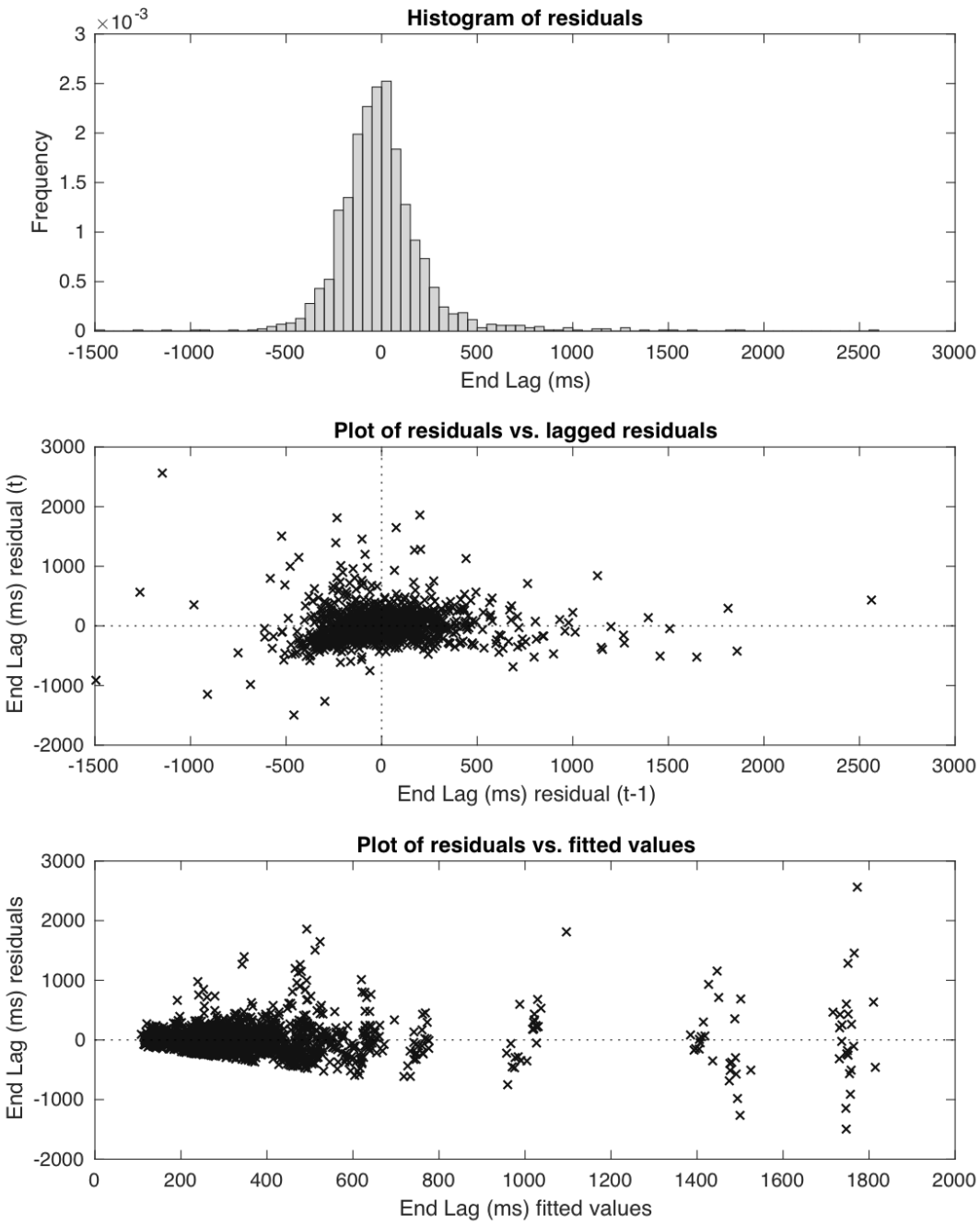


Figure 33. Residuals, end lag

7.4 Copies of published material

7.4.1 Descending motor pathways after hemispherectomy (1)

Nobbs D., Vargha-Khadem F., Cross J.H., Berthouze L., *Descending motor pathways after hemispherectomy*, 4th UK Paediatric Neuropsychology Symposium, London, UK, 2013, Poster #SP6

SP6

Descending motor pathways after hemispherectomy

D NOBBS[1], F VARGHA-KHADEM[1,2], JH CROSS[1,2], L BERTHOUZE[2,3]

[1]UCL, London, UK; [2]Great Ormond Street Hospital, London, UK; [3]University of Sussex, Brighton, UK

Background: Some patients retain contralesional hand and wrist strength after hemispherectomy. It is unknown which descending motor pathway drives these muscles.

Methods: We obtained surface electromyography (EMG) recordings from a patient who had suffered an ischaemic stroke during the third trimester of pregnancy and subsequently underwent hemispherectomy for intractable epilepsy. Unusually, she retained contralesional hand and wrist function after the operation. For comparison we also obtained recordings from two healthy controls, matched by age and sex. From all subjects, EMG was obtained simultaneously from left and right wrist extensors during voluntary contraction. The left and right EMG recordings were analysed using a time domain measure of correlation (cumulant analysis).

Results: The EMG recordings obtained from the patient were significantly correlated, with a narrow peak around time zero. This indicated short-term synchronisation of left and right motor units. When the same analysis was repeated on the control data, no significant correlation was found.

Discussion: Short-term synchronisation between motor units has been shown to signify common physiological drive. We hypothesise that, in response to the congenital lesion, crossed corticospinal neurones from the intact cortex developed abnormally, branching to target motor units on both sides of the spinal cord. Such a pattern of adaptation may explain the patient's remarkably preserved hand function.

7.4.2 Descending motor pathways after hemispherectomy (2)

Nobbs D., Vargha-Khadem F., Cross J.H., Berthouze L., *Descending motor pathways after hemispherectomy*, UCL Neuroscience Symposium, London, UK, 2014, Poster #61

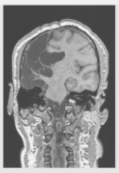
Descending motor pathways after hemispherectomy

D Nobbs[1], F Vargha-Khadem[1,2], JH Cross[1,2], L Berthouze[1,3]

[1] UCL, London, UK; [2] Great Ormond Street Hospital, London, UK;
[3] University of Sussex, Brighton, UK

UCL

Background



- Some patients retain contralesional hand function after hemispherectomy
- Motor commands driving this hand must descend from the intact cortex, although the path to the spinal cord is unknown
- Within this group, mirror movements are common, although not universal. In congenital cerebral palsy, they are caused by bilateral drive from the intact hemisphere (Carr et al., 1993; Farmer et al, 1991)
- It has therefore been proposed that, after hemispherectomy, motor commands travel along a common corticospinal pathway that branches to innervate both sides of the spinal cord
- Short-term synchronisation in the firing of two motor units (dashed line in figure) indicates common drive (bold lines) and can be determined with EMG

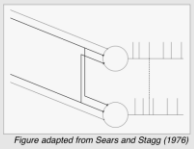
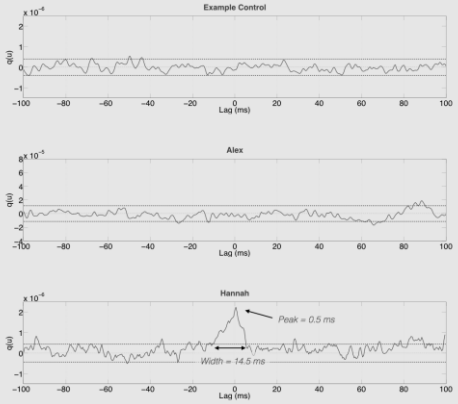


Figure adapted from Sears and Stagg (1976)

- We therefore hypothesised that hemispherectomised patients with and without mirror movements can be distinguished by the presence or absence of short-term synchronisation between bilateral EMG

Results

- Hannah's recordings were significantly correlated (see dashed lines in plots for 95% confidence intervals) over a lag range of 14.5 ms, with the strength of the association (q(u)) peaking at 0.5 ms (short-term synchronisation)
- No significant correlation was found in the data obtained from Alex or control participants (no synchronisation)



Methods

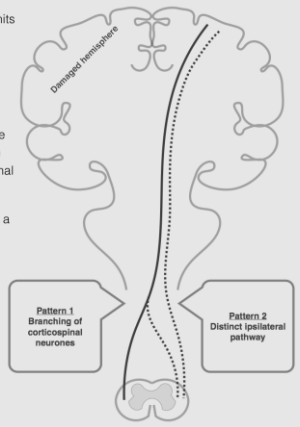
- We acquired data from two patients and four healthy controls:
  - Patient 1, Hannah, suffered an ischaemic stroke during the third trimester of pregnancy and has marked mirror movements
  - Patient 2, Alex, suffers from Sturge-Weber syndrome and does not have mirror movements
- Both patients retained contralesional hand function after left-sided hemispherectomy
- Participants extended both wrists while we recorded bilateral surface EMG
- To determine if the muscles were driven by a common input, we computed the cumulant density, a measure of pairwise linear association with confidence values
- A peak in the cumulant density is associated with a lag which denotes the delay between signals at which synchronisation occurs

This work was supported by a Child Health Research Appeal Trust studentship

Great Ormond Street Hospital Charity

Discussion

- These results indicate that, for Hannah, left and right motor units share a common drive
- For Alex these drives may be entirely distinct
- In Hannah's case we suggest corticospinal neurones from the intact hemisphere branched to innervate both sides of the spinal cord
- In Alex's case we propose that a distinct ipsilateral pathway developed
- Why the motor system developed so differently in these two patients will require further investigation



References
Farmer et al., 1991, Neurology 41: 1505
Carr et al., 1993, Brain 116: 1223
Sears and Stagg, 1976, J. of Physiology 263: 357

7.4.3 Can a single hemisphere control a bimanual action?

Nobbs D., Hammett L., Berthouze L., Vargha-Khadem F., *Can a single hemisphere control a bimanual action?*, Society for Neuroscience Annual Meeting, Washington DC, USA, 2014, Poster #7296

Can a single hemisphere control a bimanual action?

D Nobbs[1], L Hammett[1], L Berthouze[1,2], F Vargha-Khadem[1,3]

[1] UCL, London, UK; [2] University of Sussex, Brighton, UK;
[3] Great Ormond Street Hospital, London, UK

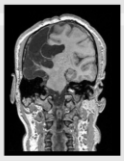
UCL

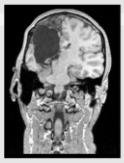
Introduction

- Jackson et al. (2000) found that a patient with central deafferentation, caused by parietal stroke at 72 years, tended to perform an asymmetric bimanual action as separate unimanual movements
- They proposed asymmetric action depends on kinaesthesia for parallel monitoring of both arms
- Hung et al. (2004) also found this in cerebral palsy, though details of brain injury were not reported
- Congenital unilateral lesions can cause the intact hemisphere to assume functions of the other side
- If damage occurs early, can the intact hemisphere assume this bimanual ability?
- We studied patients with pre/perinatal brain damage who later underwent hemispherectomy (HS). These patients have hemiparesis, hemianopia and hemianaesthesia (Holloway et al., 2000)

We asked three questions:

- Do HS patients have difficulty producing overlapping bimanual movement?
- In controls, is this ability dependent on vision?
- Do HS patients depend more on visual feedback to move the arms in tandem?





Alex

- *Age at testing:* 33 years
- *Aetiology:* Sturge-Weber with port wine stain over left forehead and eyelid
- *Hemispherectomy:* 8.5 years
- *Fugl-Meyer Assessment (paretic):* 34/66
- *Action Research Arm Test (paretic):* 26/57
- *Power Grip Strength (paretic):* 5 kg

Joe

- *Age at at testing:* 20 years
- *Aetiology:* Early MCA infarct (< 9 months)
- *Hemispherotomy:* 15yrs
- *Fugl-Meyer Assessment (paretic):* 33/66
- *Action Research Arm Test (paretic):* 19/57
- *Power Grip Strength (paretic):* Not possible

Methods

Acquisition

- We studied two patients (Alex and Joe) and ten age-matched controls
- Markers were attached to forearms and recorded with motion capture cameras (Qualisys, Sweden)
- Participants pressed an empty soap dispenser at their natural pace, twelve times with the right hand, then with the left, placing the other hand below the spout
- They repeated this blindfolded. All four conditions were repeated

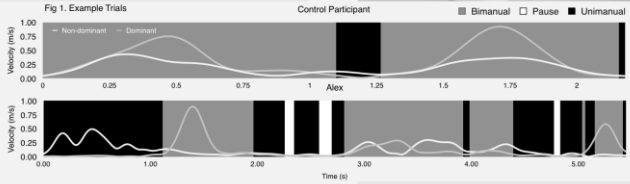
Analysis

- *Analysis 1:* we analysed all conditions; *Analysis 2:* we compared no blindfold to blindfolded
- To account for any sampling bias caused by repeated measures, the control analysis took into account subject, trial number and block number as random effects
- An arm was considered moving when its tangential velocity exceeded 5% of its maximum
- We calculated trial duration, average velocity and percent of trial in: bimanual phase; unimanual phase; pausing both arms in-between movements.

Analysis of controls
A linear mixed-effects model was fitted, with arm role and visual feedback as fixed effects and subject*block number*trial as a random effect (SPSS, IBM, US). Five measures were analysed, hence the significance threshold was adjusted to $p = .05/5 = 0.01$

Analysis of patients
We compared controls to patients in terms of mean values

Fig 1. Example Trials — Control Participant — Bimanual ☐ Pause ■ Unimanual



Analysis 1: All Conditions

Fig 2. Trial Duration

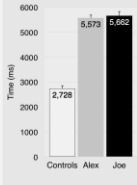


Fig 3. Trial Phases

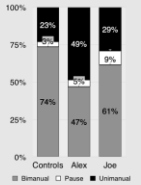
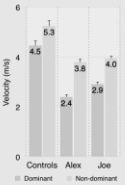


Fig 4. Velocity



Error bars represent 1 SE

Analysis 2: Difference Between No Blindfold and Blindfolded

Fig 5. Trial Duration

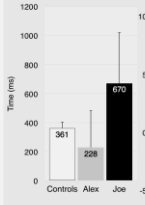


Fig 6. Bimanual Phase

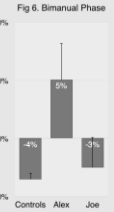
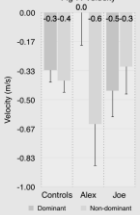


Fig 7. Velocity



Results

Analysis 1: under all conditions (Figures 2-4)

Compared to controls, Alex and Joe:

- Took longer to perform the task
- Had a shorter bimanual phase (in percentage terms)
- Moved their arms at a lower velocity

Analysis 2: difference between no blindfold and blindfolded (Figures 5-6)

Controls:
Longer trial duration ($F(1,11.25) = 68.30$, $p < 0.0001$)
Shorter bimanual phase ($F(1,20.15) = 24.40$, $p < 0.0001$)
Lower velocity Dom: ($F(1,13.45) = 16.59$, $p = 0.0002$); NonDom: ($F(1,12.97) = 27.95$, $p = 0.0001$)

Alex:
Longer trial duration, but effect was less than controls
Longer bimanual phase, unlike controls
Lower velocity of paretic (non-dominant) arm; little effect on velocity of less affected (dominant) arm

Joe:
Longer trial duration, greater than controls
Shorter bimanual phase, similar to controls
Lower velocity of both arms, similar to controls

Discussion

Do HS patients have difficulty producing overlapping bimanual movement?

- Yes. Our evidence suggests that this function cannot be performed normally by a single hemisphere, even in cases of early brain damage

In controls, is this ability dependent on vision?

- Yes. The bimanual phase was reduced when control subjects were blindfolded
- However, there was only one target - if left and right hands had separate targets that couldn't be viewed simultaneously, would controls rely more on kinaesthesia?

Do HS patients depend more on visual feedback to move the arms in tandem?

- The blindfolding effect was similar for Joe and controls. This suggests reduced kinaesthesic feedback did not cause a greater dependence on visual feedback
- For Alex, the blindfold effect was less. This may indicate a greater visual deficit and may explain the consistently lower bimanual phase. This could be related to the port wine stain over his eyelid

Conclusion: The ability to overlap left and right arm movements is impaired in hemispherectomised patients. We suggest this is due to reduced sensory information - both visual and kinaesthetic.

References: Jackson et al. (2000) *Brain*, 123, 380-393; Hung et al. (2004) *Dev. Med & Child Neurology*, 46, 746-753; Holloway et al., (2000) *Brain*, 123, 2432-2444

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